DISSERTATION ON

RELATIONSHIP OF MICROALBUMINURIA WITH ISCHAEMIC HEART DISEASE IN NON DIABETICS

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfilment of the regulations
for the award of the degree of

M.D. DEGREE IN GENERAL MEDICINE

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Thanjavur Medical College

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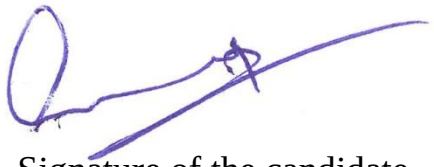
DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled RELATIONSHIP OF MICROALBUMINURIA WITH ISCHAEMIC HEART DISEASE IN NON DIABETICS is a bonafide and genuine research work carried out by me in the Department of General Medicine, Thanjavur Medical College.



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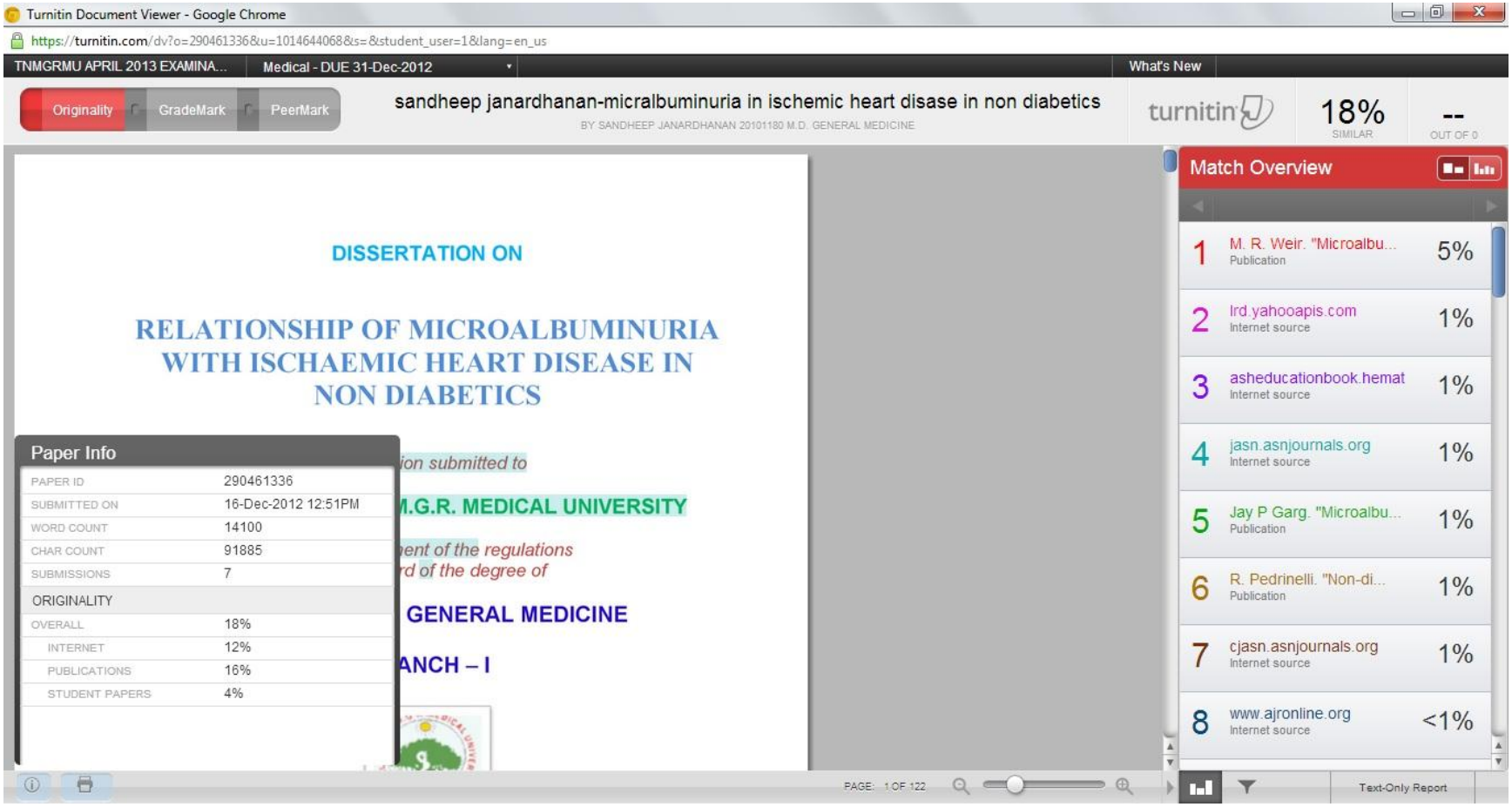
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ABSTRACT

BACKGROUND AND OBJECTIVE

Microalbuminuria has been an established indicator for micro and macrovascular pathology in diabetics. But there is growing evidence that microalbuminuria may be an important indicator of future chance of developing coronary arterial disease. This study was conducted to establish a relationship between microalburminuria and Ischemic cardiac Disease in non-diabetics.

METHODOLOGY

50 randomly selected non-diabetic patients with Ischemic Heart Disease who fulfilled the criteria for the study were evaluated for traditional risk factors and microalbuminuria in Thanjavur Medical College.

RESULTS

Microalbuminuria was detected in 38 (76%) patients with Ischemic Heart Disease ($p < 0.001$). 76.4% patients with infarct pattern on ECG and 75% patients with ischemia pattern on ECG had microalbuminuria. Majority of patients had microalbuminuria levels between 30-50 mg/day (43.2% males and 46.2% females). 84.7% of female patients had microalbuminuria compared to 73% of the male patients. 79% of hypertensive patients had microalbuminuria compared to 71% of normotensive patients. 77.8% of

smokers with microalbuminuria presented with myocardial infarction compared to 54.5% of non-smokers with microalbuminuria.

INTERPRETATION AND CONCLUSION

Our patients with ischemic heart disease had a significantly positive association with microalbuminuria. Hence, microalbuminuria can be regarded as an additional risk factor for ischemic heart disease.

KEY WORDS:

Ischemic Heart Disease; Cardiovascular disease, Microalbuminuria; ECG; Enzyme Linked Immunosorbent Assay; HDL, LDL.

INTRODUCTION

Ischemic Heart Disease which has an estimated prevalence of 6-9% in the general population in India may become the leading cause of death and impairment in our country by the year 2018.

Since The remarkable research conducted by Framingham trials, many cohort based and cross sectional studies have determined a group of non dependent risk factors for ischemic heart disease among which age, male gender a previous familial history of young ischemic heart disease, history of cigarette smoke and , history of diabetes mellitus, systemic ,hypertension, hypercholesterolemia, hypertriglyceridemia and low incidence of good(HDL) cholesterol is taken as colloquial risk determinants.

There has been an interest in increasing cardiovascular risk assessment, as a result of better knowledge of the pathophysiology of phenomenon called atherosclerosis and novel sites for anti-ischemic drug treatment has been identified .This has stimulated the quest for new risk factors.

One such novel risk factor is microalbuminuria which has emerged as an independent and robust risk factor. Microalbuminuria has been historically accepted as an indicator for microvascular and macro vascular pathology in diabetes mellitus patients. However there has been more evidence is pointing out to the fact that microalbuminuria is a significant cardiac risk factor even among general population.

The inclusion of microalbuminuria which is an easy to obtain indicator along with the classical risk factors may improve risk stratification.

The present study is being conducted to define the micro albuminuria prevalence among non-diabetics patients of Ischemic Heart Disease drawn from lower middle and upper lower class of South Indian population admitted to the Thanjavur medical college Thanjavur and outpatients attending the outpatient wing of the Department Of Internal Medicine and cardiology in Thanjavur medical college, Thanjavur

OBJECTIVES

1. To estimate microalbuminuria in non-diabetics having evidence Ischemic cardiac Disease.
2. To study the relation of micro albuminuria with Ischemic cardiac Disease in these subjects.

REVIEW OF LITERATURE

Ischemic Heart Disease

Ischemic refers to a deficiency of oxygen as a result of inadequate blood supply to the myocardium, which causes a mismatch between oxygen demand and supply . The commonest cause of myocardial ischemia is atherosclerotic obstructive disease of epicardial coronary arterial system.

Atherosclerosis-Pathogenesis

The term "atherosclerosis" was introduced by Marchand who described the relation of fatty sclerosis with vessel wall sclerosis. The phenomenon afflicts large-sized and medium and small vessels and made remarkable by discrete intramural subintimal sclerosis which encroaches on lumen of the arteries

The characteristic lesion of atherosclerosis has three major parts. The first of the three is cellular part which has a majority of smooth myocytes fibroblasts and monocyte macrophage complex. The second part is composed of connective tissue with extracellular matrix and lipid cellular layer[1].

The third component is the lipid layer in intracellular region which accumulates inside macrophages, as a result changing the macrophages to foam cells. Lesions of atherosclerosis are due to result of inflammatory reactions, subsequent massive cytokine release and multiplication of smooth myocytes, connective tissue extracellular matrix synthesis, and accumulation of lipids and macrophages and fibroblasts.

The forerunner of Atherogenesis: Endothelial Insult

The inner lumen of a ordinary human arteriole has a covering made of endothelium monolayer which adheres to the endothelial layer

The cells of endothelium give the vessel with a non occlusive layer; platelet aggregation retarded by presence of negative charge which endothelium process and endothelial secretion of inhibitors prostacyclin (PGI) and also endothelial relaxation factor known as (EDRF-NO). PGI_2 along with EDRF-NO, secreted by endothelial cells, have relaxation effect on smooth myocytes in tunica media[2].

The cell of endothelium produces chemicals that antagonize smooth myocyte proliferation and transfer these cytokines like heparan sulfate chondritoin sulfate and EDRF-NO. Lastly, cells of endothelium protect the vessel with a lumen layer to whom macrophages platelets and lymphocytes cannot stick. Cells of endothelium which are injured are morphologically distinct from ordinary endothelium. As distinct from normal, they typically does not having same alignment as blood flow direction and they have lesser attachments between cells, causing augmented permeability.

The endothelial cells which are injured also have thrombotic tendency when compared with normal cells because of the decreased synthesis of EDRF-NO and PGI2. Ischemic endothelium accelerate vascular smooth myocyte transfer and multiplication by secreting less relaxation factor by releasing platelet-derived like growth factor (PDGF), prostacyclins and endothelin-2 and endothelin-1. also, ischemic endothelium help the transfer of monocytes by releasing monocyte chemo attractive protein-1, , and adherence using surface receptors like selectins, with which macrophages will attach[3].

ROLE IN INFLAMMATION, ENDOTHELIAL DAMAGE AND MECHANISM OF LIPIDS

The slowly progressive atherosclerotic phenomenon is conspicuous, in the early times, by disruption in endothelium function. Atherogenesis is started as cellular layer of endothelium over-express adhering molecules as a response to turbulence in flow of blood in presence of unfavourable lipid profile .Li et al showed that VCAM-1 expression on endothelium was an Necessary process in the development of atherogenesis[4].

DIAGRAM OF NORMAL MUSCULAR ARTERY

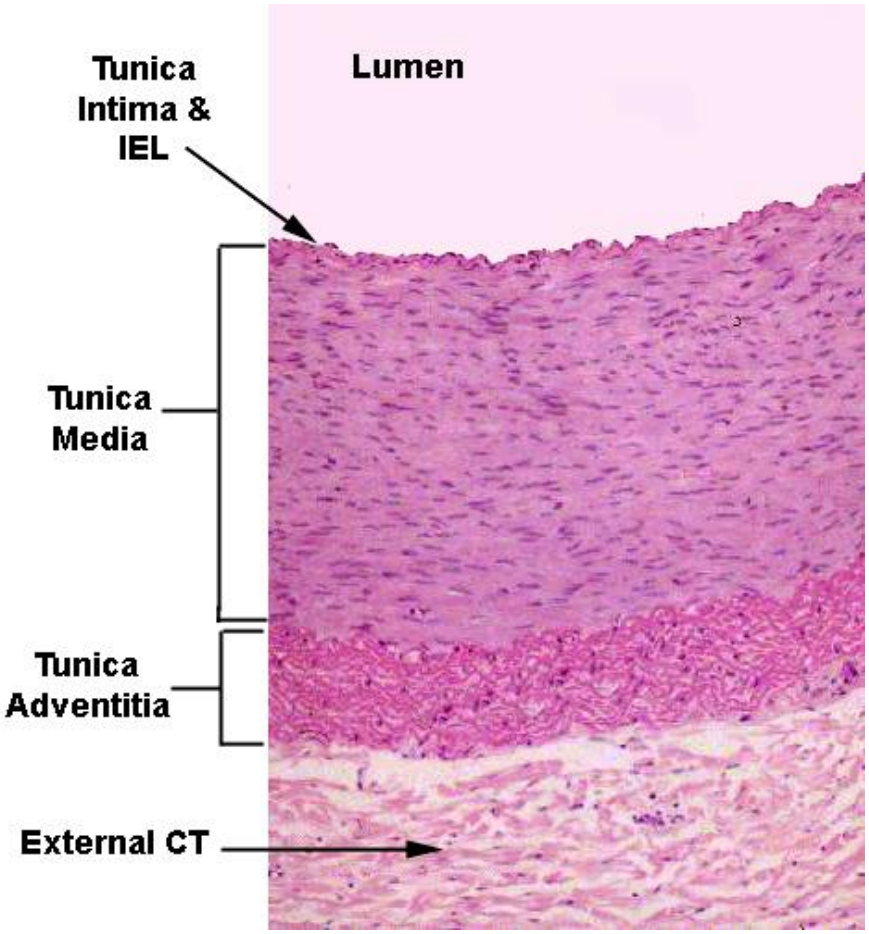


Diagram of Normal Muscular Artery showing outer tunica externa, Middle, media and inner endothelial layer. with internal elastic lamina(IEL)and outside connective tissue(CT)

Enhanced cellular level adherence and co existing endothelial dysfunction then results in for the aggregation of inflammatory chemicals, cytokines release and aggregation of lipid molecules into the pathogenic plaque.

INFLAMMATION AND CHRONIC ENDOTHELIAL INJURY

Now it is generally believed that early progress of pathogenesis of atherosclerosis are controlled, largely, as a result of inflammatory cascade. VCAM-1 attachment aggravates transfer of subsequently when endothelium is injured then secretion of monocyte chemo-attracting protein (MCP-1) by polymorphs amplifies inflammatory cascade with recruitment of additional cells , stimulating polymorphs in the layer of tunica media, and resulting in transfer and subsequent growth of smooth myocytes. As a response to signs created inside the early plaque of atheroma, monocytes attach to the endothelial layer and subsequently get transferred trough the intimal layer and underlying basement membrane by expressing enzymes, which include regionally generated matrix metalloproteinase enzymes (MMP) which destroy connective tissue network[5] .

Transferred monocytes secrete additional hormones start travelling through the endothelial surface into tunica media. This phenomenon is still aggravated by the local secretion of monocyte-colony stimulating factor (M-CSF), which results macrophage proliferation; local stimulation of monocytes macrophage leading to cytokine- mediated progress of atherosclerosis, and oxidative damage of low-density lipoprotein (LDL).

Lots of inflammatory mediators is known to affect the plaque development in atherosclerosis. For instance CD40L which was elaborated inside the atheromatous plaque was known to hike the secretion of tissue activating factor (and , in all means enhance the possibility of thrombosis) in atherosclerotic plaques due to atherosclerosis ; anti- CD40L negates evolution of existing lesions of atherosclerosis in animal trial models[6,7].

Inflammatory cytokines elaborated by myocytes inside the plaque due to atherosclerosis include, but are not confined to, interleukins (IL)-1ß, tumor necrosis factor (TNF) and ß, , MCP-1, IL-18 GM-CSF and CD-40.

The effect of the cytokines is vast and include, cellular matrix proliferation, mitogenesis new and vessel generation and foam cell growth at steaks are often the first recognizable atherosclerotic lesion usually are seen first in the surroundings of vessel branch sites where abnormal hemodynamic shearing stresses result in capillary damage [11]. Fat streaks are mainly flat lesions, in tunica intima comprising of smooth muscle cells and macrophages and which contain lipid drops s which give the the tissue a foam like morphology[8] .

Forerunners of these insults, macroscopic type I, , lesion, may be seen among infants as young as one years. Fatty streaks normally show at places at where capillary insult has aggravated capillary leakage enough to let in LDL(low- density protein) and other large molecules to permeate the endothelium.

Once below the endothelium, LDL (low-density lipoprotein), has a big liking for amino sugars and, become sequestrated. LDL (Low-density lipoprotein) go through sequence of changes which cause the production of modified variety of LDL (low-density protein.)[9]

This change of LDL(low-density lipoprotein) is important for at three causes is a chemical attractant molecules, with monocyte chemo attractant protein(MCP) relased by injured capillary cells, transfer circulating macrophages to the subendothelium, where they metamorphose into macrophage. Monocyte transfer is controlled by aggregation molecules and –capillary l mediated leukocyte sticking and chemo attractant molecules.

Also vessel cell adherence to molecule- is expressed in lumen of damaged endothelium..Also, new LDL (low-density protein) prevent the exodus of phagocytes from the site. Last, importantly change of LDL (low-density protein) helps tissue to draw huge quantities of fat laden cells

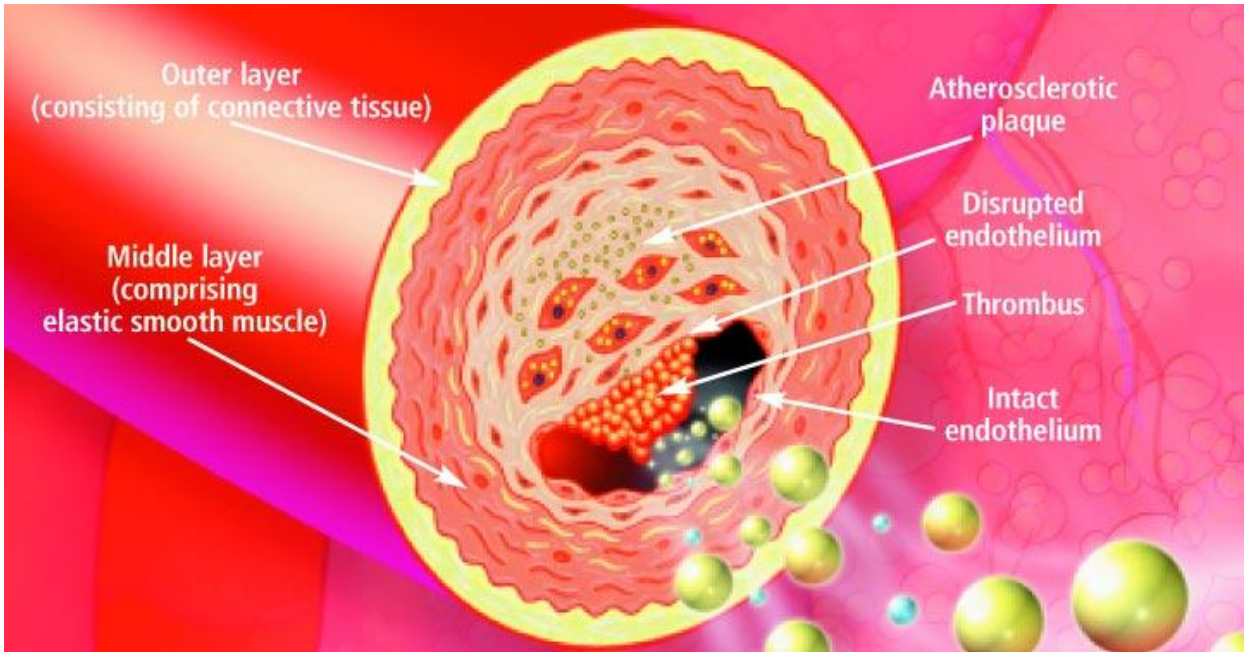
Formation of fibrotic areas

The next step in the pathogenesis of a lesion of atherosclerosis is change of the streak to a fibrous plaque like lesion. Fibrous type of injury are composed of fibrous cap made of myocytes transferred from underneath endothelium and tunica media.

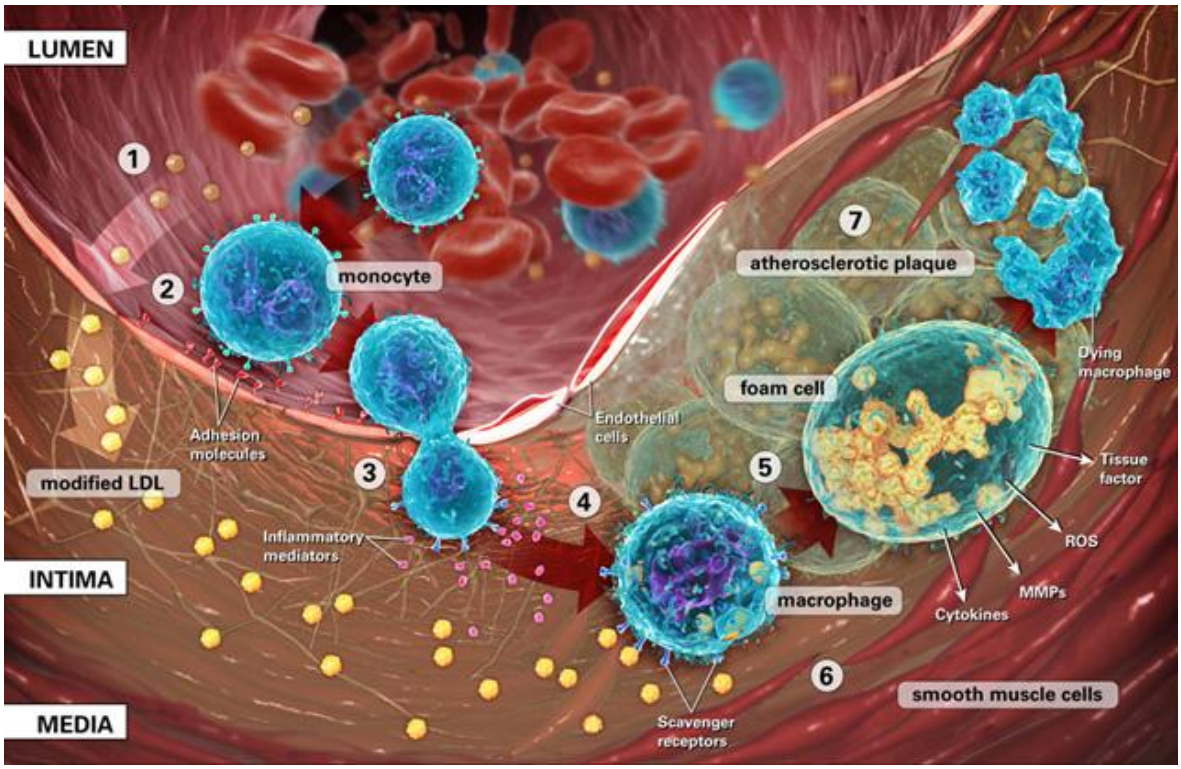
Other components of the fibrous cap consist of non functional endothelium on Lumen of the fibrous cap, monocyte macrophages, platelets and T cell. Undreneath fibrous cap, fibrous injury is made of lipid cells of monocyte macrophage and myocyte origin.

One of the initial incidents causing change of steak to fibrous lesion constitutes focal destruction endothelium which covers the lipid steak. This is caused by shear stress exerted on the non functioning tissues from derangement of the vessel tissue wall and from radicals produced in the body (free radicals and products of lipid peroxidation)secreted by underlying foam cells.

CROSS SECTION OF A ARTERIAL LUMEN DISRUPTED BY ARTHEROSCLEROTIC PLAQUE



MOLECULAR MEDIATORS OF DEVELOPMENT OF ATHEROSCLEROTIC PLAQUE



AUTOPSY SPECIMEN OF A LARGE ARTERY DESTROYED BY PROGRESSIVE ATHEROSCLEROSIS

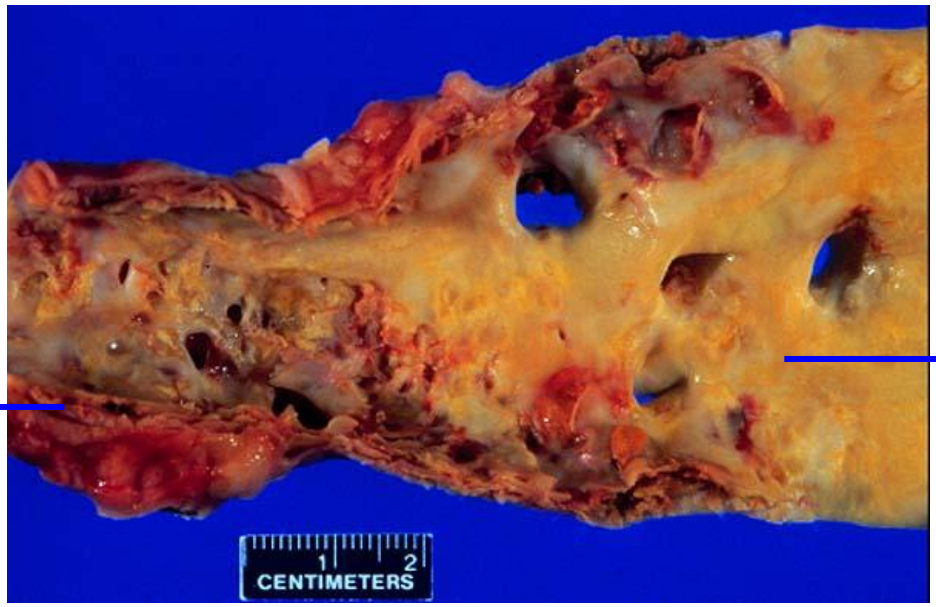
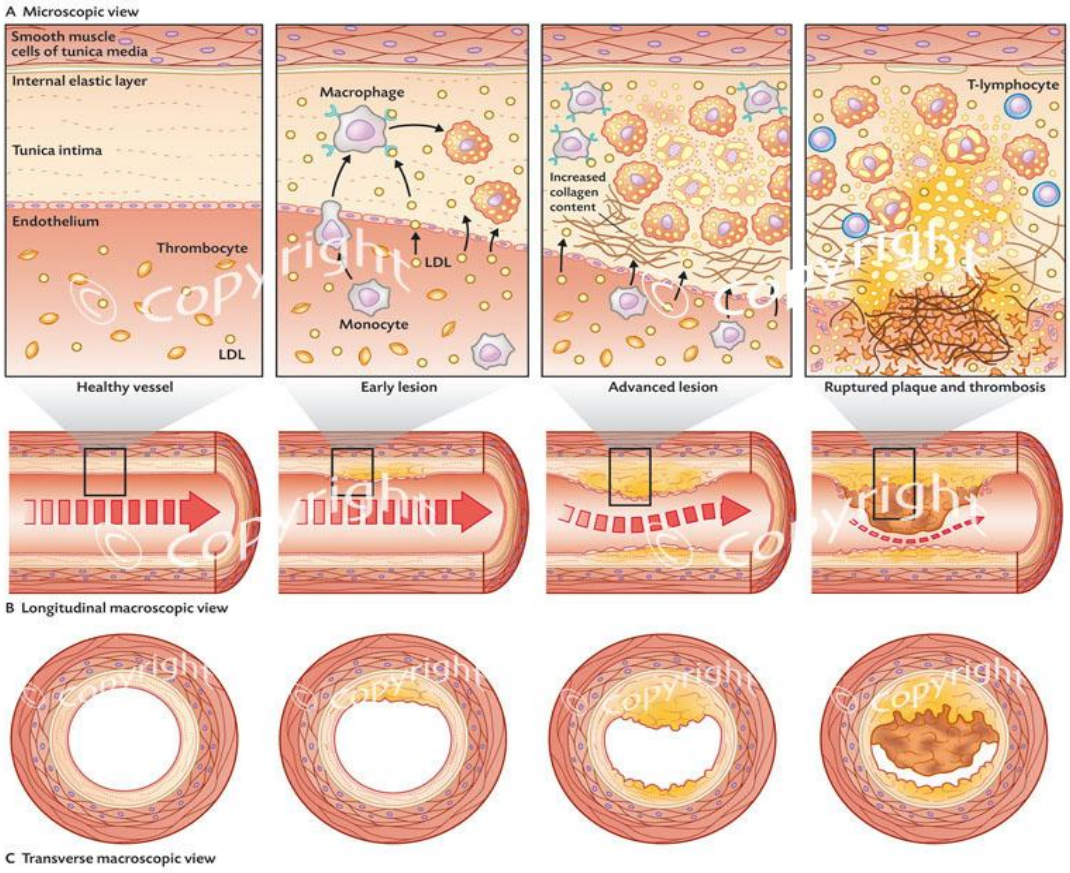


ILLUSTRATION SHOWING PROGRESIVE PLAQUE LESION AND ADVANCEMENT OF ARTERIAL LUMEN NARROWING



FINAL STAGES OF PLAQUE DEVELOPMENT

One of the last step of pathogenesis of the injury is the metamorphosation of the fibrous plaque to advanced plaque, where a thrombotic plaque has developed later due to atherosclerotic plaque ulceration or as a result of intra plaque haemorrhage. Factors causing plaque fracture compose turbulence and mechanical shearing stress, bleeding into plaque due to breakage of the small arteries and , increased vessel lumen strain on the fibrous tip due to the existence of the pre existing lipid pool, along with secretion of extracellular tissue -destroying enzymes by monocytes which have a presence inside the lesion[10].

THE ROLE PLAYED BY LIPIDS

The fat and lipid hypothesis which is proposed as a cause of atherosclerosis has been drastically modified over the period of last twenty years. Once seen as the initial part of atherosclerosis, it has now been accepted that internalisation and aggregation of lipid starts in response to initial alterations in the vessel wall endothelial pathology.

Lipid Accumulation is, hitherto, needed for the growth and development of the definite plaque. Lipid deposits are initially started with the LDL movement starting from blood stream into blood vessels. Once it reaches inside the tunica media three types of fate can occur to LDL: it can return to blood stream (a feature of plaque regression and a process which will be helped by some fat lowering measures), it can be oxidized (with help of molecules like free radicals or as a result of direct activity of polymorphs) or it may be endocytosed by monocyte and then is converted into foam cells.peroxidized LDL can be notoriously atherosclerotic and has affinity for fibroblasts and- macrophages.

Monocyte system Monocytes Macrophages attach to intimal LDL through group of new receptors also known by the name scavenger receptor, identifying LDL after the molecule is per oxidized. Intake of peroxidized LDL makes the monocytes less active, hence promotes the aggregation of the fat-filled cells of the tunica intima.

The lipid laden foam cells regain the activeness and release wide variety of chemokines and other inflammatory cells.

Results of the aggregation include transfer with aggregation of smooth myocytes to elaborate more locally acting chemokines), further LDL destruction and peroxidation, deployment and transfer of extra macrophages and monocyte/lipid laden cells with further destruction and damage and impairment of endothelial cell function.

Some plaques proliferate inside the plaque, probably in response to local angiogenic cascade The potential significance of phenomenon called angiogenesis in pathophysiology of atherosclerosis is demonstrated in experiments that which show anti angiogenic treatment decreased atheromatous lesion progress in a placebo control trial in atherosclerosis pathology prone mice

Two types of plaque destruction are seen: superfluous injury& deep injury. The first type injury results in patchy regions of focal endothelial destruction which grow leading to the Development of mural and even adhesive thrombus. Plaques that are filled with collagen tissue, delineated by huge amount of lipid-laden macrophage monocytes which tend to lead to superficial insults[11] .

Deep vessel insult is conspicuous by a split or shear which extends from lumen of plaque into substance of the plaque. This type of insult, occur in plaque which has a large fat-rich pool, exposing blood and its components to the highly thrombotic contents that makes up the plaque.

Thrombus activation can affect the course of the phenomenon called atherogenesis; in presence of an emergency like myocardial infarction and unstable angina caused due to release of chemokines like von Wile brand tissue factor-controlled platelet aggregation adhesion .and activation

PREVENTION AND EPIDEMIOLOGY OF ATHEROSCLEROSIS

Atherosclerosis which is a multifactorial entity whose age of start and progress are greatly influenced by a plethora of inborn and acquired risk**.** Since the exemplerary work of the Framingham trials, various prospective trials and clinical and non clinical studies have identified a group of risk factors for myocardial infarction, and peripheral vascular disease**,** and stroke among which the pre-existence of atherosclerotic vascular disease, age, male sex similar history of premature atherosclerotic disease in

family ,history of smoking**,** history of diabetes mellitus, hypertension, history of dyslipidemia and low serum HDL cholesterol have been considered as colloquial risk determinants[12].

In recent past results of two randomized control trials involving of more than 600000 candidates in 16 assessment trials and four observational trials have proved that that 70-80% of patients who later had significant ischemic heart pathology had at least two of four colloquial risk determinants viz dyslipidemia (blood cholesterol >250mg /dl /6.22 mmol/l), hypertension (systolic BP >146 mm Hg and/or diastolic BP >94 mm Hg), prevalence of diabetes mellitus and history of smoking. A single risk determinant doesn't carry much weight but a combination of various risk factors carry great importance .hence at this point of time the best way to asses the risk is to tabulate the determinants in a an algorithm and then statistically asses the risk.

This method has been taken as the best means to asses the whether a person will have an ischemic insult to heart within next ten years many algorithms has been developed worldwide but best of them are FRAMINGHAM GUIDELINES from USA and Germanys PROCAM

trial[14, 15]. Various current guidelines have made their recommendations first starting lipid lowering therapy and BP lowering therapy depending on global risk stratification.

Even with best screening algorithms the chance of detecting people with low risk of cardiac illness will require cost intensive screening of big populations. But in such situations presence of high false positive results lead to wrong treatment given to general public**.**

The growing interest worldwide in improving cardiovascular risk assessment and preventing cardiac morbidity and mortality resulting from a better knowledge of natural course of the of atheroma s and identifying of novel targets for anti-atherogenesis drug had resulted in search for novel risks. Many cross sectional cohort and randomized control studies have shown existence of several biomarkers with ischemic heart disease. Unfortunately most of the markers were not reproducible in further studies and most of them were inter related to classical risk factors but nowadays some of these markers appear to be genuinely independent and not dependent on classic risk factors.

Here there is an active debate ranging about their utility in routine risk assessment. Of all these most important are Lp (a), homocysteine micro albuminuria fibrinogen and CRP[13]

LIPROTEIN (A)

A consensus about the standardisation has only been recently recognized and hence it use as a marker is still in rudimentary stages. Now a days most labs take a standard of 30 ng/ml above which risk of ischemic heart disease is to be suspected in spite its high genetic predisposition of blood Lp (a) levels. It doesn't have much intraindividual changes but, renal impairment and overt excretion of protein

It will result in high serum LP (a). In other words serum Lp (a) level doesn't have much significance but prevalence of variability of its protein ingredient, apolipoprotein (a), ultimately determine susceptibility of a person towards cardiac illness

C-REACTIVE PROTEIN

CRP levels more than 1 mg/l has been associated with mild risk while a level above 3mg/l has been associated with significant risk of ischemic heart disease. But CRP LEVELS is affected by BOTH types of inflammation and it is not unusual to find levels of more than 10 mg/ml and still patient in good shape [16].

FIBRINOGEN

Fibrinogen assays like CRP AND LP (a) have not been standardized internationally. Citrate is needed in the anayzlate which makes cumbersome specimen. Also fibrinogen is an acute phase marker; hence it is virtually useless in patients having acute and chronic inflammation.

MICROALBUMINURIA DEFINITION OF MICROALBUMINURIA

A broad definition for micro albuminuria was adopted in 1995 which determined it as abnormal in individuals with impaired glycemic metabolism as an abnormal elimination of albumin falling within the range of 25-200 microgram/minute or instead taken as 30-300 milligram/day.36 this definition still holds good and may be applied for all patients without regarding their co morbid conditions[17].

It was following research of Viberti and colleagues that the word MA has come into existence but still the so defined Levels of microalbuminuria is an artificial group which is composed of continuum results[14, 18].

All the public screening and survey data has shown the fact that microalbuminuria has been related to an augmented risk for generalized mortality and morbidity, strokes(cerebrovascular disease,) and, probably implicated in the pathogenesis of, peripheral arterial mortality causing diseases

As a result of 7 year follow up study of apparently healthy subjects (without co morbid factors like diabetes, hypertension and CVD), the chance of with the level of UAE not developing cardiac pathology showed a linear relation in the whole study population and also in the cohort of subjects having albumin excretion just below the minimum cut off for microalbuminuria.

In the Heart Outcome and Prevention Evaluation (HOPE) study, UAE urinary albumin excretion) did predict chance of mortality in subjects With more than 55 yr age with CAD and diabetes with minimum one more cardiovascular risk determinant).the causes of death due to all causes was 9.5% in subjects not having microalbuminuria *viz* 18.%in the group having

microalbuminuria ([RR] 3.11% 95% confidence level [CI] 2.85to 3.39). A direct association was observed with the microalbuminuria and cardiac pathologies, which extend beneath the normal threshold of microalbuminuria

The incidence of microalbuminuria does seem to foretell all round reasons of death in the public populace. the amazing fact was first depicted by Prevention of the Reno Vascular End stages Diseases (PREVEND) trial , where natives of city of Groningen, Nederland, in the age group 29 to 77 yr were given a verbal question bank and provided bottle to catch the first -morning urine clean catch sample for assessment of urinary albuminary excretion(UAE)[19].

A gross number of 40 ,458 candidates were prospectively assessed for a time period of 2.8 yr were made the part of study And detailed analysis of death by measurement of base urinary albuminary excretion (UAE.)

There seem to be a valid positive association of urinary albuminary excretion(UAE) and all reasons of death due to cardiac and non cardiac illness Microalbuminuria does seem to have an association with various cardiovascular abnormalities, which include left ventricle chamber (LV) dysfunction and hyperplasia holter monitoring defects, and existence coronary artery Heart Disease (CAHD).

The Strong Heart TRIAL did show a relation of microalbuminuria and abnormal echocardiographic parameters of both RV and LV systolic and diastolic work assessment in a group of 1578 indigenous Americans with impaired glycemic tolerance.[20]

Table 1: Clinical studies reporting the risks associated with a positive microalbuminuria result

(A) Prospective studies

No	Study	Microalbuminuria Definition	Population	Risk Associated with a Positive Microalbuminuri Result (95% CI)
1	Prospective studies HOPE	ACR >=2 mg/mmol in a first morning spot urine sample	Subjects at high cardiovascular risk >=55 yr with CVD or with diabetes +>=1 CVD risk factor; n = 9043)	All-cause mortality: RR 2.09 (1.84 to 2.38)
2	PREVEND	UAE 20 to 200 mg/L in an early morning spot urine sample	Residents of Gronngen, the Nederland, 28 to 75 yr (n = 40,548)	Cardiovascular death: RR 1.29 (1.18 to 1.40) Non cardiovascular death: RR 1.12 (1.04 to 1.21)
3	PREVEND	UAE 30 to 300 mg in a 24-h urine Sample	Residents of Groningen, the Nederland, 28 to 75 yr (n = 7330)	All-cause mortality: HR 3.3 (1.5 to 7.1) for patients with ST-T segment changes microalbuminuria versus 0.9 (0.4 to 1.9) for ST-T segment changes alone Cardiovascular death: HR 10.4 (2.5 to 43.6) for patients with ST-T segment changes _ microalbuminuria versus 2.7(0.6 to 12.3) for ST-T segment changes alone

(B) Cross-sectional studies

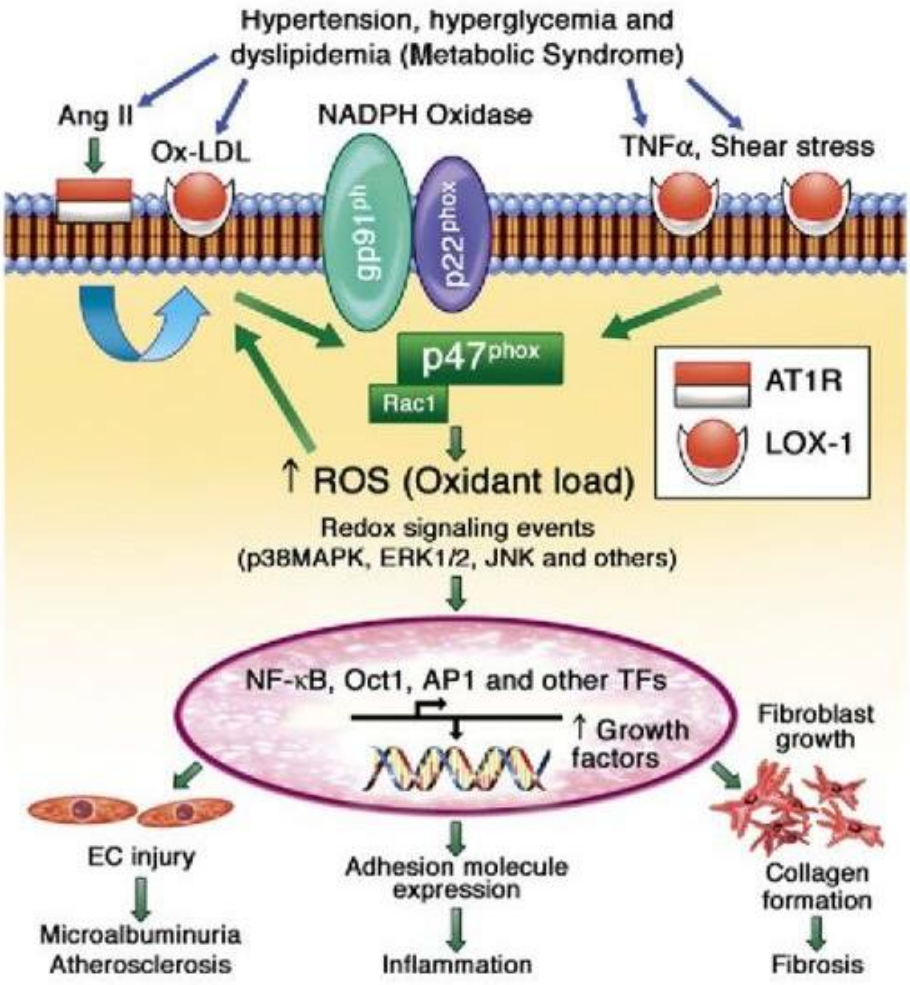
No	Study	Microalbuminuria Definition	Population	Risk Associated with a Positive Microalbuminuri Result (95% CI)
4	Hoorn Study	ACR >= mg/mmol in a first morning spot urine sample	Population-based: White individuals, 50 to 75 yr (n = 631)	Cardiovascular death: RR 3.22 (1.28 to 8.06) All- cause mortality: RR 1.70 (0.86 to 3.34) All-cause mortality in patients with hypertension: RR 2.87 (1.22 to 6.33)
5	HUNT	ACR >=76 mg/mmol (_60th percentile) in a first-morning spot urine sample	Nondiabetic, nonhypertensive residents of Nord- røndelag,Norway, >=20 yr (n =2089)	All-cause mortality: RR 2.3 (1.0 to 5.4)
6	EPIC-Norfolk	ACR 2.5 to 25 mg/mmol in a random spot urine sample	Residents of Norfolk, UK, 40 to 79 yr (n = 20,911)	All-cause mortality: HR 1.48 (1.20 to 1.79)Cardiovascular death: HR 2.03 (1.55 to 2.67) Fatal stroke: HR 1.58 (1.10 to 3.0)Coronary heart disease death: HR 2.01 (1.40 to 2.90
7	EPIC-Norfolk	ACR 2.5 to 25 mg/mmol in a random spot urine sample	Residents of Norfolk, UK, 40 to 79 yr (n _=23,630)	Stroke: HR 1.49 (1.13 to 2.14)
8	Third Copenhagen City Heart Study	UAE >.8 _g/min (> 3rd quartile) in a timed overnight urine sample	Residents of Copenhagen, Denmark, 30 to 70 yr, without coronary heart disease	All-cause mortality: RR 1.9 (1.5 to 2.4) Coronary heart disease: RR 2.0 (1.4 to 3.0)
9	Danish MONICA	ACR >0.65 mg/mmol (>90thpercentile) in a first-morning spot urine sample	Population-based: Individuals without Ischemic Heart Disease, renal disease, urinary tractinfection, or diabetes (n =2085))	Ischemic Heart Disease: RR 2.3 (1.3 to 3.9)
10	Shibata Study	Positive albumin dipstick test	Residents of Shibata, Japan, >40 yr (n = 2651)	Stroke: RR in men 2.5 (1.1 to 5.7
11	Portland Study	UAE 20 to 200 mg/L in a first morning spot urine sample)	Older residents of Portland,oregon,with previous stroke or transient ischemic attack (n =121)	Recurrent stroke: HR 4.9 (1.4 to 17.6)

No	Study	Microalbuminuria Definition	Population	Risk Associated with a Positive Microalbuminuri Result (95% CI)
12	Slowik et al.	UAE 30 to 300 mg in a 24-h urine Sample	Patients admitted within 24 h of *A first ischeic stroke (n = 60)*	Mortality: OR 6.0 (1.3 to 27.7)
13	Cross-sectional studies Zander *et al.*	UAE 20 to 200 mg/L in an early morning spot urine sample	Patients with type 2 diabetes (*n* =1060)	PAD: OR 2.1 (1.4 to 3.2)
14	PREVEND	UAE 30 to 300 mg in a 24-h urine sample	Nondiabetic residents of Groningen, (, 28 to 75 yr(*n* = 7579)	Electrocardiographic abnormalities: Infarct patterns: OR 1.61 (1.12 to 2.32) Major ischemia: OR 1.43 (1.08 to 1.91) Minor ischemia: OR 1.32 (1.03 to 1.68)
15	PREVEND	UAE 30 to 300 mg in a 24-h urine sample	Nondiabeticresidents of Groningen,the Netherlands, 28 to 75 yr (*n* = 6669)	PAD: OR 0.98 (0.68 to 1.41) in multivariate analysis
16	Earle *et al.*	UAE 20 to 200 _g/min in a timed overnight urine sample	Patients with type 1 diabetes and without CVD	Silent myocardial ischemia: OR 6.3 (1.2 to 37.8)

Most of the albumin which has been filtered is reabsorbed by the proximal tubule via low capacity phagocytic process. About 15-28mg/24h of albumin which will be present in urine. if we calculate that about 8 gramme of albumin is processed every day, a unit hike in generalized vascular permissiveness of system the in response to an insult or a injury would cause an extra 75 mg of albumin which gets through the filters .already corrective mechanisms for tubular reabsorption of albumin have been exhausted completely so this will cause, urinary albumin excretion hike from a range of 30 to around 120 mg in 24 hours.[21]

Nephronal permissiveness to albumin is related to not only charge selectivity present on endothelium but also selectivity regarding the size. The nephronal membranes will have a negative charge by its constituent glycoproteins plays which help in preventing in loss of anions .it has also been noted that there is a decrease in nephronal charge selectivity in subjects with microalbuminuria regardless whether they are diabetic or non diabetic.

ILLUSTRATION OF THE VICIOUS CYCLE BY WHICH MICROALBUMINURIA CAUSE ENDOTHELIAL INJURY AND ENDORGAN DAMAGE (MOLECULAR PATHWAY)



Also changes in the amount of plasma processed by the nephrons due to variations in glomerular blood pressure regulation will cause relatively huge variations in amount of albumin excretion.

Microalbuminuria may be a indicator of generalized vascular pathology, with arterial endothelial dysfunction being involved in the pathogenesis of atherothrombotic vascular disease.

At present there is no consensus of opinion regarding exactly how MA causes or accentuates atheroma formation and subsequent degeneration. but at present it is widely assumed that mechanisms of vessel toxicity related with MA are distinct from those subjects with or without diabetes and who have co existing hypertension.[22]

In patients with MA who are not suffering from diabetes, the endothelial malfunction and changes in the cellular involvement will lead to to a hike in vascular leakage and as result accentuates the degenerative process. Of atherosclerosis abnormal endothelial leakage causes lipid influx into the tunica media and intima of vessel causing degenerative changes at present it is assumed that MA won't be directly implicated in the pathogenesis of nondiabetic vascular or renal disease solely due to hypertension. This ambiguity will help us relate to association that the albumin moiety doesn't have a glycated form

Table 2: Pathologic steps in relation with MA

Local STEPS 1. Elevated intraglomerular capillary oncotic pressure 2. Accentuated transport of albumin mediated through pores in glomerulus
Systemic steps 1. Inflammatory mediator's activation cascade 2. Elevated intracapillary albumin leakage 3. Endothelium malfunction of the vessels

Table 3: Factors influencing the MA development.

1. High quetlet index(BMI)
2. Elevated bp(systolic and diastolic)
3. Dyslipidemia
4. Resistance to insulin (syndrome X)
5. Cigarette and beedi abuse
6. Exaggerated sensitivity to salt
7. Old age
8. Endothelium mal function

The endothelium synthesis proteins of the cellular matrix and help synthesis of several important cardiac and renal proteins. An mismatch between normal endothelial and absence of homeostasis between vasodilatation and anti thrombosis is a main reason causing atheromas. hence it has been assumed that defective permeability of endothelium may be cause of the of MA in the general population, in the patients with systemic hypertension, and patients with diabetes. Even though malfunction of endothelium is not a distinct process, several analysis and observations suggest that endothelial dysfunction may show a common pathogenesis for both micro and macro vascular morbidities[23].

Endothelial dysfunction will have a key role in (non- diabetic causes of atherosclerosis. Altered permissiveness of the intima permits lipoproteins (oxidized LDL) to enter into the large blood vessels and help in the growth of plaques. the accentuation in vascular leakage accompanied with decreased response of beta-receptor results in impaired insulin action by preventing insulin-helped skeletal myocyte vasodilation which interferes with insulin associated glucose re uptake.

Micro albuminaria is related with biochemical indices of endothelial malfunction like elevated von Willebrand factor and accentuated platelet aggregation.

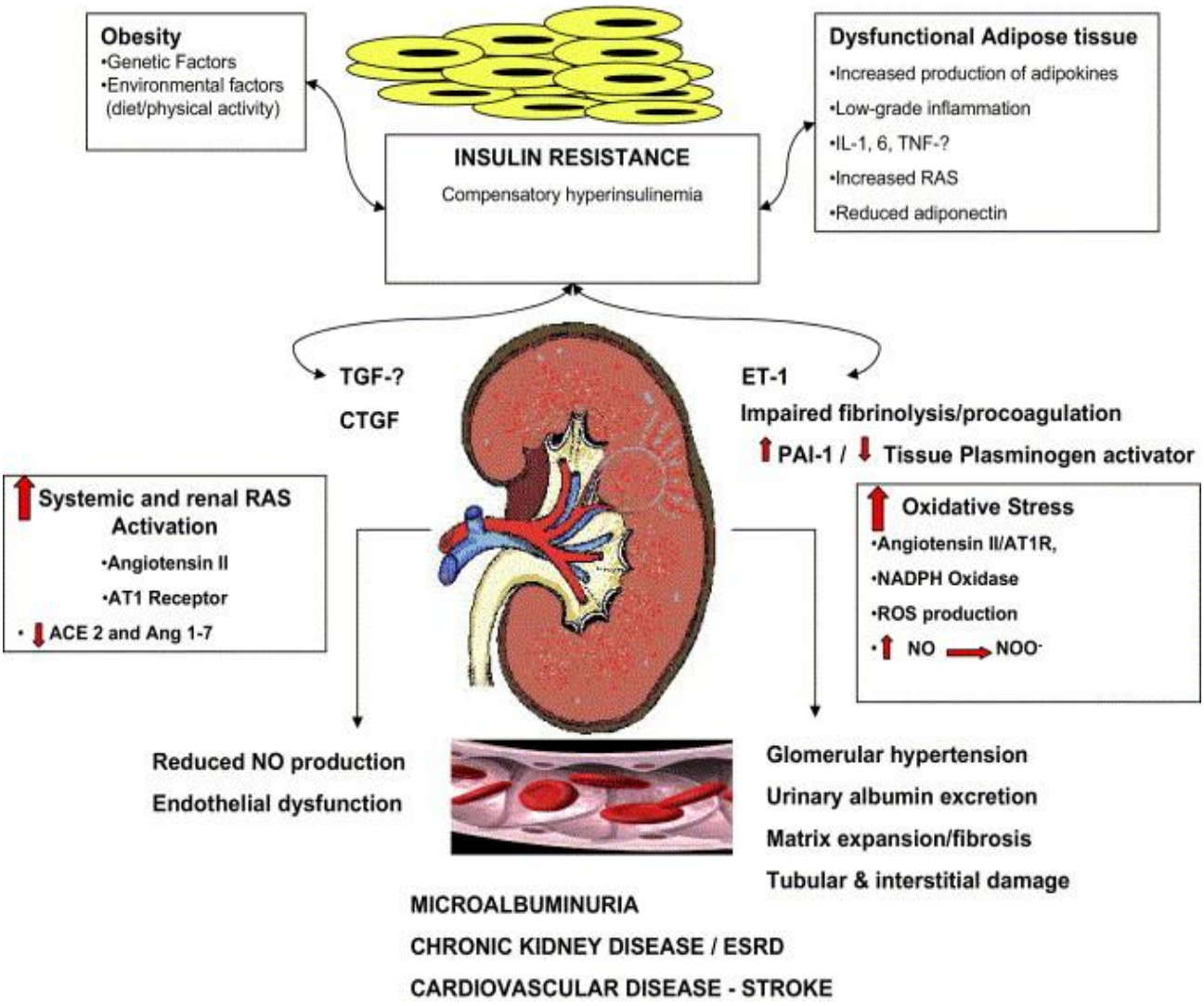
It was observed that in both non-diabetic subjects with essential hypertension and diabetic patients participants having microalbuminuria had elevated plasma levels of vWF antigen than patients having normal albumin excretion.

Other biochemical indices of endothelial malfunctioning include increase in the Serum levels of angiotensin II, PA) and thrombotic profile consisting of plasminogen activator and inhibitor–1 (PAI-1) and new molecule called endothelin[24].

So it can be assumed that endothelial malfunction play a important part in) glomerulosclerosis in non diabetics, MA assisted insulin sensitivity and development of atherosclerosis.

MA is an early indicator of target end organ damage related with CVD but has been related with accentuated cardiac mortality and morbidity in non diabetics Aggerwall and co workers showed a significantly higher occurrence of ischemic heart disease CVA, and peripheral diseases in arteries in patients with MA

MULTIPLE EFFECTS OF MICROALBUMINURIA ON VARIOUS SYSTEMS



MA has a direct relation with severity of morbidity. The conditions which follow this dictum are reperfusion and ischemia. MA has also seen in the setting of an acute infarction of myocardium and peripheral arterial disease and has direct relation with severity of the infarct or severity of claudication. The STENO theory forwarded by Deckard and colleagues. Albumin leak into the urine reflects generalized vessel damage. Hence the nephron is the assumed as key part of the vessel system[25].

In lieu of the theories of endothelial mal function and chronic persistent inflammation are possible ways to arrive at a link of micro albuminuria and ischemic heart disease. But there are many discrepancies in the texts.

Even though it's right that persistent inflammation can be cause and a endothelial malfunction, some trials used markers such as, TNF-α IL-1, IL-6, which suggest that persistent inflammation is associated with progression of microalbuminuria and which is related with an increased chance for atherosclerotic vessel damage. but another group of trials show that though microalbuminuria, endothelial dysfunction, and persistent and low-grade inflammation are having links, they are also considered as independent risk factor cardiac mortality[26].

Many cross-sectional case control and cohort and prospective trials showed that microalbuminuria was having relation with many cardiac risk determinants like age, history of hypertension, history of diabetes, history

of smoking, prevalence of obesity, and abnormal lipid profile these explain, only a very small portion of the relation of micro albuminuria with atheromatous events.

Hence with regard to endothelium function and inflammation there is a chance that this will cause both microalbuminuria along with ischemic heart disease yet a another hypothesis is that most of the people having varying degree of vessel derangement within normal range and, hence, eliminate a varying quantity of micro albumin. This existing vagarisms of the vessel wall state can be assessed by urine micro albumin elimination which may be related with chance of further end organ damage. This explains why micro albuminuria is good predictive marker of both ischemic heart disease and recent-onset systemic hypertension and glycemic impairment. In this scenario, then it is advisable to mark these susceptible to asses early primary prevention in such a scenario, the renal system may serve as an approximate measure of BP ; that is, target BP where normal urinary albumin excretion is present also, intensive.

Sugar control and aggressive control of LDL if coexisting with stabilization of albumin elimination will be a suitable marker of prognosis as far as therapy is concerned[27].

Yudkkin et al were did a cohort study of MA(24-hour daytime UAE $\geq$ 30 microgram/min) with assessment of cardiovascular and peripheral vessel disease risk in a cohort of 189 patients (58 diabetic or impaired glycemic tolerance) in the Islllington Diabetes trials

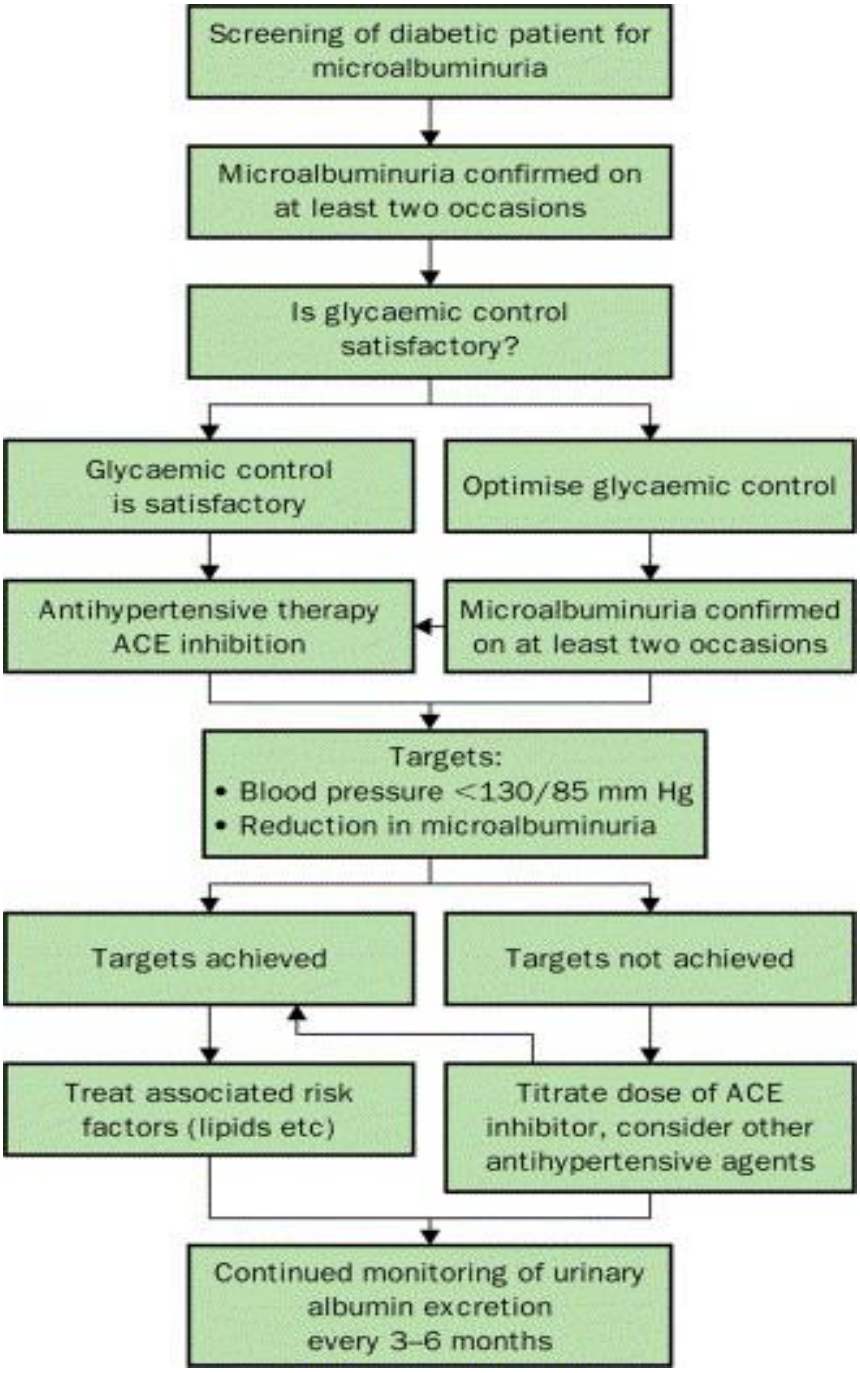
In the cohort study , Yudkkin et al demonstrated a independent relation of MA with prevalence of all-cause morbidity and mortality [7/19 (34.12%)] vs. [3/148 (2.03%)]normal albumin excreting individuals in 167patients after a median 3.7years follow-up [33].

Table 4: List comparing horizontal (C) and cohort (P) trials showing Microalbuminuria in non diabetics and urinary albumin excretion used as predictor of cardiac pathology

No	Author/ref.	year	No	Design	End-point	Population
1	Yudkin	1988	187	P	ECG changes Incidence of MI PVD and angina	Diabetics,IGT,NON diabetic patients
2	Haffner	1990	316	P	MI	Normal subjects
3	Damsgaard	1999	217	C	Deaths in total	Normal subjects
4	Winocour	1999	448	p	Ecg changes	both patients
5	Damsgaard	1992	218	C	ECG abnormality	Normal patients
6	Damsgaard	1998	217	C	DEATHS due to	Normal patients
7	Gould	2001	957	P	MI, PVD	Normal patients
8	Howard	2002	4569	P	Definite MI	Diabetic Americans
9	Kuusisto	1997	1079	C	Cahd fatal and non fatal	Normal patients
10	Gorgels	1994	232	C	MI and angina	Both groups
11	Agerwall	1995	119	C	Carotid atheroscerosis	94 essential hypertensives NIDDM
12	Bigazzi	1998	92	P	MI	normotensives

No	Author/ref.	Date	N	Design	End-point	Population
13	Ljungman	1996	120	P	PVD	HTNS and normal people
14	Jensen	1997	2613	P	MI	Both groups
15	Jensen	2003	1254	P	Previous CAHD	HYPERTENSIVES
16	Mykkanen	2004	1441	C	Subclinical carotid atherosclerosis	991 non-diabetic, 450 diabetic
17	Pontremoli	2002	53	C	Subclinical carotid atherosclerosis	Hyper- and normotensive subjects
18	Fabsitz	2001	4276	C	Ankle/brachial index < 0.9	American diabetics
19	Jager	1999	631	P	All CVS mortality	Both groups
20	Beamer	1999	121	P	Stroke, MI,	Diabetic and normal patients
21	Diercks	2000	7579	P	Holter changes	Normal patients
22	Gerstein	2000	5708	C	Peripheral vascular disease	Non-diabetic with cardiovascular disease
23	Jensen	2001	207	C	MI CAHD PVD	Uncomplicated hypertensive subjects
24	Pedrinelli	2000	136	C	Carotid ischemia	Uncomplicated hypertensive men
25	Roest	2001	1 118	P	MI,angina	Postmenopausal women
26	Gerstein	2001	5 545	P	All CAHD mortality	Non-diabetic with cardiovascular disease.

AN ALGORITHM FOR ASSESSMENT OF MICROALBUMINURIA IN HYPERTENSION AND DIABETES



The recently finished PREVEND trial where MA (30–300 mg/24 h) was firm and independent association with electrocardiographic prevalence of either infarction or existence of ischemia in 7589 individuals with no history of diabetes. The HOPE trial also demonstrated that MA (MA: ACR_3mg/mmol) has very crucial and independent role as predictor among 5709 individuals not having diabetes with well established vascular pathology[29].

In the American Indians who were non diabetic in the Strong Heart trials, the existence of ischemic cardiac disease, CVA, peripheral arterial disease was related with micro albuminuria prevalence (ACR - 32 and 320 mg/g) regardless of age, BP, glycemic impairment dyslipidemia along with serum fibrinogen[39]

In 1079 nondiabetic Finnish individuals from the Kuopo community who were prospectively followed up 3.5 years, the occurrence of death due to cardiac and coronary pathologies increased by twice in view of ACR $\geq$ 3.32 mg/mmol. When adjustment was done for various confounding variables, like hypertension, the relation was weakened[30, 31].

Damsgaard et al. by their pioneering research that microalbuminuria is associated with three times higher mortality.

In patients with normal sugar levels where albuminuria was equal to or well ahead of mean range (>7.62 micro g /min ;) in comparison with people below (43/109 vs. 9/108).

The relation between microalbuminuria and ischemic heart disease may not be just accidental but the two may be bound by a common pathophysiologic process. Although many deranged physiology of the vessel wall predispose to microalbuminuria and ischemic heart disease

The endothelial malfunction is taken as causative factor of atherosclerosis and is believed to have an significant role in prognosis of atherosclerotic process .hence, a relation of microalbuminuria with gross endothelial malfunction, which if is there , will explain why microalbuminuria is good marker of ischemic heart disease. also, microalbuminuria in both type of diabetes usually is associated with endothelial malfunction and, and EDRF NO synthesis and its availability and acceptability, as calculated by blood level of chemokine agents such as, tissue- plasminogen type activator, vascular cell and soluble variety of E- selectin and by endothelial-dependent dilatation of blood vessels as a response to augmentation in flow or increase in cholinergic chemicals.', hence endothelium mal function in Patients having diabetes with micro albuminuria, is exhaustive.

A small survey found an altered endothelial vascular response which was related with microalbuminuria .it was noted in the brachial renal arteries and other abdominal arteries but not much awareness is there if of any of the trials which have been carried out, for instance, in coronary vessel circulation.[32]

There are very less trial on the amount of endothelium mal function in patients who are non diabetic with micro albuminuria, but existence of endothelium mal function, in diabetes, has been theorized as to control the hemostasis regulation , and fibrinolysis system control, polymorph adhesion, EDRF NO Production s and accessibility.

For instance, one current, big, population survey of 647 subjects (median age 69 years; 249 with normal blood sugar, 139 with impaired glycemic metabolism, and 261 with history of type 2 diabetes) demonstrated that endothelial NO production, as calculated from ultrasonically calculated brachial artery endothelial flow -dependent, flow-determined dilation, was deranged in individuals with diabetes.[34]

These data stress the fact that altered endothelial EDRF NO production Has a role in the relation of microalbuminuria with all type of cardiovascular morbidity and mortality risk regardless whether glycemic impairment is present or not . also, several trials have stressed that endothelial mal function predates and foretells the start of microalbuminuria patients with and without

diabetes.

Hence it is is tempting to tell that endothelial malfunction in microalbuminuria shows why micro albuminuria has always been. a consistent and fairly accurate marker of increased probability of risk for atherothrombosis. In the past, glomerular permissivity was postulated to depend mostly on basement membrane of the glomerulus constitution and slit diaphragm morphology. current studies have shown, a significant active role of the glomerular endothelium in assessing penetration to albumin .specially, the negative charged glycocalyx that covers the endothelium fenestrations is the most significant parameter for assessing glomerular permeability and ion selectivity.[35]

Alterations in the endothelial layer of outer glycocalix will have a contribution to Micro albuminuria but this has been blamed in the pathophysiology causing atherosclerosis, which gives a potential dangerous liaison between albuminuria and probability cardiovascular morbidity and mortality · In this context recent studies probable common pathway for increased albumin leakage from glomerulus vascular disease has shown new data on the belief that micro albuminuria shows systemic flow dependent intravascular loss of albumin, resulting in preponderance to increased presence of atheromatous lipoprotein plaque molecules into arterial tunica media— Steno theory[36]

Athero thrombosis at present is considered as a phenomenon in which endothelial malfunction and, persistent inflammation are significant initial events. also, long standing low-grade degradation result in endothelial mal function, and the both of them are strongly associated long standing persistent vessel inflammation which may be gauged by measuring C-reactive protein levels in both diabetic and non diabetic patients microalbuminuria has been related with an predisposition to cardiac risk, which is independent when as compared to known risk factors.

Also microalbuminuria can be a future useful tool for improved and advanced cardiac risk assessment. Its is certain that in the co existence of microalbuminuria, strict monitoring of cardiovascular risk determinants is necessary the exact mechanism with which microalbuminuria is related to cardiac pathology risk is not known. It is not clear if at present microalbuminuria results in atheroma or the other way around .one postulation is that common risk determinant may be the real culprit for causing the relation of microalbuminuria and cardiac illness and disease, but there is no clear evidence regarding the same The relation of microalbuminuria with cardiac illness may be associated by a common pathology, like endothelial mal function and chronic, persistent inflammation. Many more trials are definitely needed to increase our knowledge in this field[37].

MONITORING, SCREENING DIAGANOSIS AND TREATMENT ALBUMINURIA

BASIC PUBLIC PERSPECTIVE

Since there is growing knowledge that healing of microalbuminuria in patients without glycemic impairment will have a cost effective alternative to prevent cardiovascular disease, all health care professionals should heed more need to the early diagnosis and further management of patients with microalbuminuria.

As of, now many antibody-tests are used to asses lower levels of both qualitative and qualitative urine albumin. These include nephelometry, ELISA. Immuno turbidimetry, RIA[38].

It has been said the gold standard diagnostic method for microalbuminuria is the radio immunoassay; many other tests which are done in standard labs are generally highly sensitive for routine clinical usage. Immuno turbidimetric test for microalbuminuria has been based on the quantification liquid phase immunoprecipitation. Antibodies against human albumin are added to an aliquot of patient urine and reaction buffer. The antibodies undergo an agglutination reaction with albumin in urine, resulting in an increase in turbidity of the mixture. Turbidity is measured using a clinical chemistry analysis at a wavelength of Ca 405 nm.

MICROALBUMINURIA KIT SHOWING TEST STRIPS, AUTOANALYZER AND TESTING FOR MICROALBUMINURIA

In the recent past, a novel way was started with which both immunoreactive and immuno unreactive albumin. can be measured. Previously only one type could be assessed with this type of test, large number of patients hitherto not overtly albuminuric were found to have protein excretion in microalbuminuric range[40].

But at present it is not known that the patients who have been screened by the novel method are having the same risk. But it is prudent to. measure albuminuria in fresh sample than old sample

For a long time Because of the effort involved, even though not the method of choice for it has been accepted that gold standard test for micro albuminaria is 24 hr urine sample screening. But in practice this carries lot of difficulties. The next best option is timed urine collected overnight. This also runs into practical difficulties because this demands urine collection over a given time, this may be used for high risk screening specific groups such as patients with diabetes or hypertension, hitherto it is not practical for general public screening. Another option is first-morning urinary sample. This has the certain good points compared to a spot-urine sample since it mostly always done at the same time of that particular day , and it not that much affected by patients status and if patient engages in any physical activity, which will negate the variance influenced by the above two determinants[41].

But in actual clinics, a spot-urinary sample is gathered when the subject sees the physician or at the primary health centre where the sample is collected.

In order to quantify albuminuria, usually the elimination of albumin in unit time has to be assessed: UEA IN a 24 hour sample or it may be calculated per minute (as in regarding timed night samples). Regarding untimed collection, it's better to assess the spot albumin : creatinine proportion

The introduction of albumin--creatinine proportion creates a different problem as it necessitates, use of varying. Terminologies for abnormal results for males and females Also, creatinine elimination are dependent not gender but age and race. So its better to do a urinary albumin assessment from a spot collection is equally good for the assessment of microalbuminuria in terms of albumin creatinine proportion[42].

Table 5: Classification of abnormal urinary albumin excretion

	24 Urine Albumin (mg/24 h)	Overnight Urine Albumin (microg/min)	Spot Urine			
			Albumin (mg/L)	Alb/Creatinine proportion		
				Gender	mg/mmol	mg/g
Normal	<15	<10	<10	M	<1.30	<11
				female	<1.77	<16
High limit	16 to <30	11 to <21	11 to <21	M	1.25 to <2.5	10 to <20
				F	1.76 to <3.5	15 to <29
Micro albuminuria	32 to <299	22 to <100	22 to <220	M	2.6 to 26	20 to <200
				F	3.6 to 36	30 to <300
Macroalbuminuria	>300	>200	>200	M	>25	>200
				F	>35	>300

Ideally if a patient is having positive microalbuminuria he should be repeatedly screened. Ideally test should be twice or thrice repeated. its taken as positive if best of three values is positive[43, 44]

It has been recently surmised that occurrence of micro albuminaria may precede the occurrence of overt glycemic impairment and systemic hypertension. Micro albuminaria has also been hypothesized as a warning sign for insulin resistance. It has also been shown that the quantitative excretion of microalbuminuria has a direct relationship as overt manifestation of metabolic syndrome X manifests. All this leads us to doubt whether micro albuminaria can be used a determination and screening tool for various non communicable diseases rather than treating it as an innocent bystander[45].

METHODOLOGY

Study Design

Randomised hospital based study.

Study subjects

Fifty (50) non-diabetic subjects with Ischemic Heart Disease attending the outpatient clinic or admitted as inpatients in the Department of Medicine and cardiology wards,

Inclusion Criteria

The diagnosis of Ischemic Heart Disease was based on the 12 lead ECG and exercise thread mill testing (in two subjects), cardiac enzyme estimation and the Rose questionnaire. Also echocardiogram was done to asses ejection fraction

Exclusion Criteria

1. Diabetic patients by ADA criteria (2004).
2. Congestive cardiac failure as presentation.
3. Urine showing
    - Macro albuminuria (dipstick positive albuminuria)
    - RBCs > 50/µl
    - Leucocytes > 75/µl

4. Female patients with vaginal discharge.

Method of collection of data

This was a hospital based retrospective study involving 50 patients. Data collection was by clinical history, examination and investigations. These details were recorded as per the proforma attached as annexure.

The patients included in the study were first self reported, infarct pattern, major or minor ischemia by ECG or TMT positive for inducible ischemia. Cardiac enzyme estimation was done. Echo cardiography was employed to measure the ejection fraction.

The patients were given a container for collection of urine over 24 hours which was then sent for estimation of microalbuminuria level by immune turbidimetry method. The result was reported as x mg/day of albumin.

Statistical Analysis

The data is presented as Mean ± SD. The limit of significance was calculated using SPSS Version 15 software.

Statistical Software

Both MS word and excel of windows 7 ultimate were extensively utilized for drawing graphs, tables, etc. Statistical software namely ANOVA & SPSS Version 16 was used for the analysis of data.

RESULTS

Fifty (50) patients fulfilling the criteria for the study were included. The study was done over a period of one and half years. Data was collected as per the proforma attached.

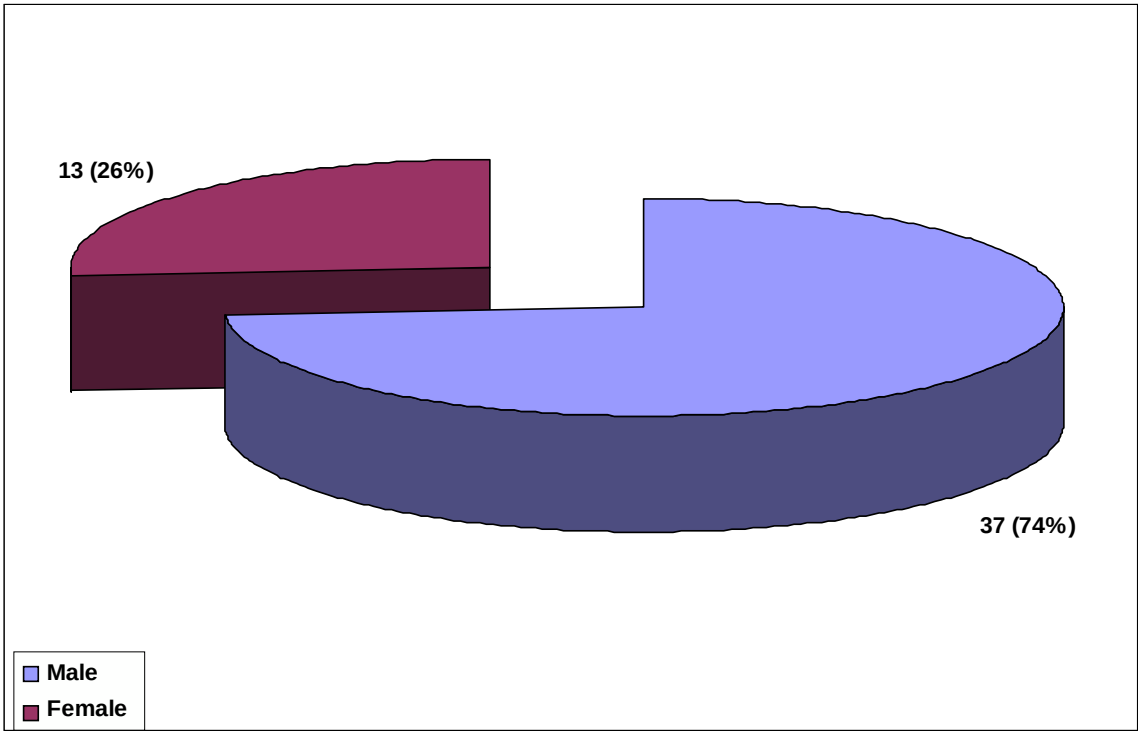
1) Sex distribution

In the present study, out of 50 patients, 37 were males and 13 were females.

Table 6: Sex distribution in study subjects

Sex	Number of patients	Percentage
Male	37	74
Female	13	26

Figure 5: Sex distribution in study subjects



Male to female ratio was 2.85:1 in the study.

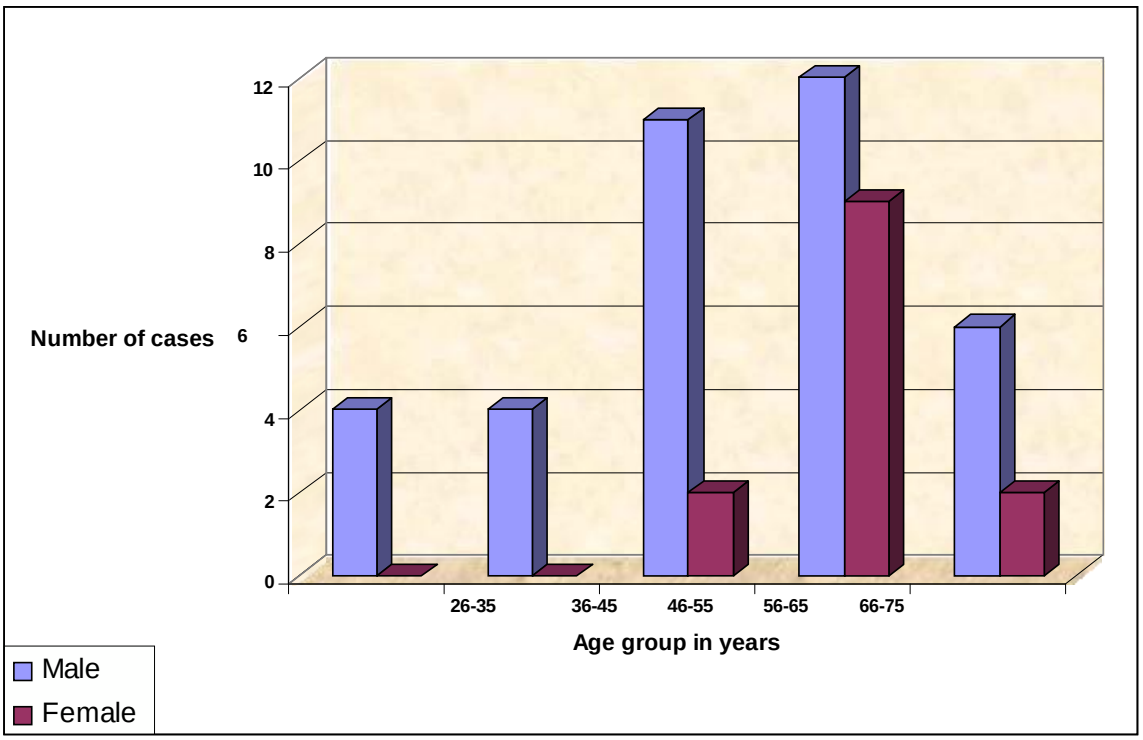
2) Age distribution in the study subjects

Table 7: Age distribution in the study subjects

Age	Sex		Total
	Male	Female	
26-35	4	0	4
36-45	4	0	4
46-55	11	2	13
56-65	12	9	21
66-75	6	2	8
Total	37	13	50

The mean average age of the study group was 55.68 ± 11.10 years. It was 54 ± 19 years for male and 59.92 ± 6.42 for females. Subject in the age group 56-65 constituted 42% of the study group. Majority of females were aged above 55 years (84.61%).

Figure 6: Age distribution in the study subjects



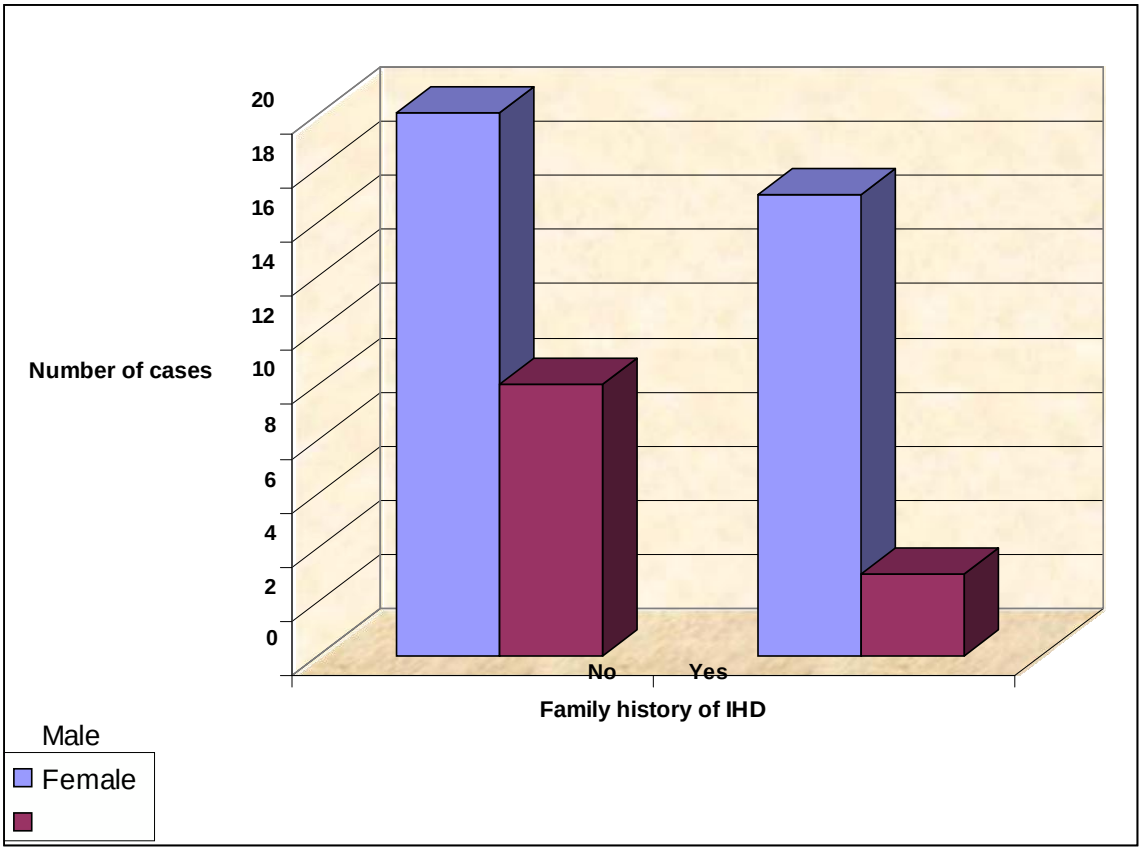
3) Family history of Ischemic Heart Disease

Table 8: Family history of Ischemic Heart Disease

Family history of IHD	Sex		Total
	Male (n=37)	Female (n=13)	
No	20	10	30
Yes	17	3	20

A positive history of IHD was present in 40% of the study subjects.

Figure 7: Family history of Ischemic Heart Disease



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4) History of current smoking

Table 9: Patients with history of smoking

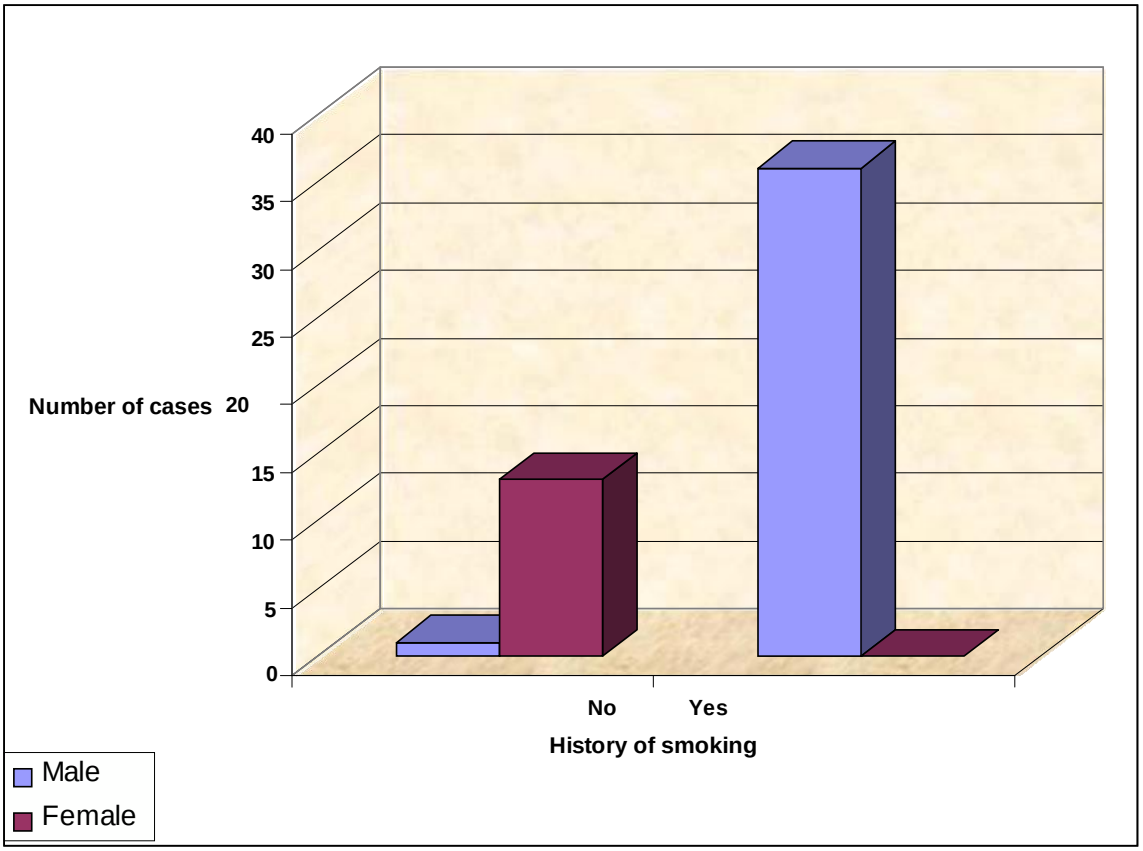
History of smoking	Sex		Total
	Male (n=37)	Female (n=13)	
No	1	13	14
Yes	36	0	36

χ^2 – 9.680; p<0.002

There was no female patient with history of smoking whereas 97.3% of the male patients gave a history of smoking.

Smoking history was present in 72% of the study subjects (P<0.002) which was statistically significant.

Figure 8: Patients with history of smoking



5) Body Mass Index

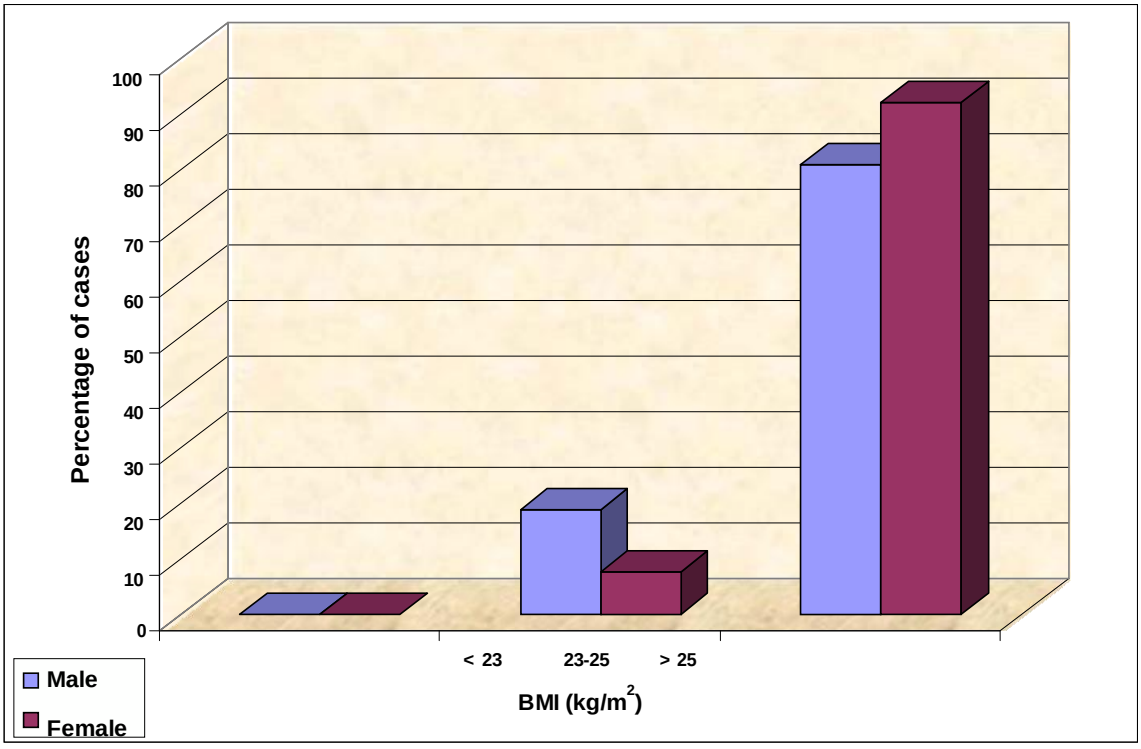
Table 10: Distribution of BMI

BMI (kg/m^2)	Males (n=37)	Female (n=13)	Total
< 23	0	0	0
23-25	7 (18.9%)	1 (7.7%)	8 (16.0%)
> 25	30 (81.1%)	12 (92.3%)	42 (84.0%)

χ^2 –23.12; p<0.00

The mean BMI was 25.87± 0.96 in males and 27.76 ± 2.17 in females. Majority of the patients were obese (84%). Female patients had a higher incidence of obesity in the present study.

Figure 9: Distribution of BMI



6) Hypertension

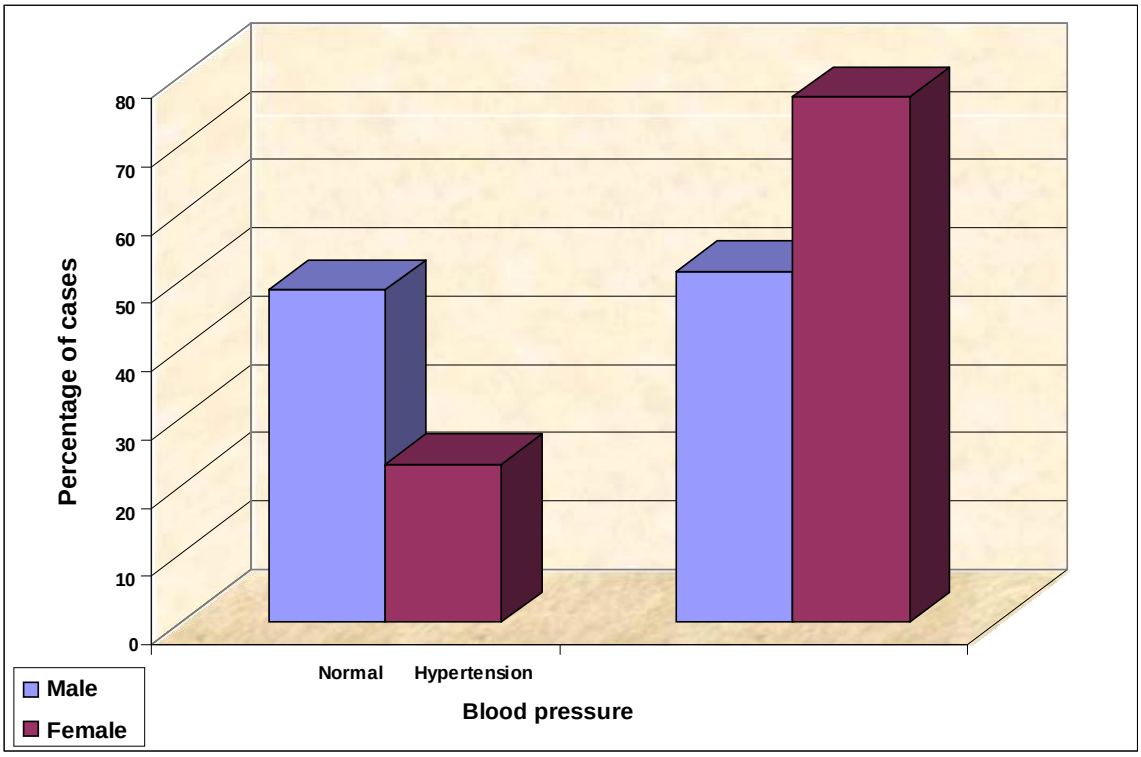
Table 11: Patients with Hypertension in the present study

BP	Sex		Total (n=50)
	Male (n=37)	Female (n=13)	
Normal	18 (48.6%)	3 (23.1%)	21
Hypertension	19 (51.4%)	10 (76.9%)	29

χ^2 – 1.280; p<0.25

Hypertension was present in 58% of the study subjects of which females had a higher percentage (Male to Female – 51.4% to 76.9%). The mean systolic BP was 144.81± 10.84 in males and 148± 8.97 in females. The mean diastolic BP was 88.86± 6.84 in males and 90.0 ± 8.16 in females.

Figure 10: Patients with Hypertension in the present study



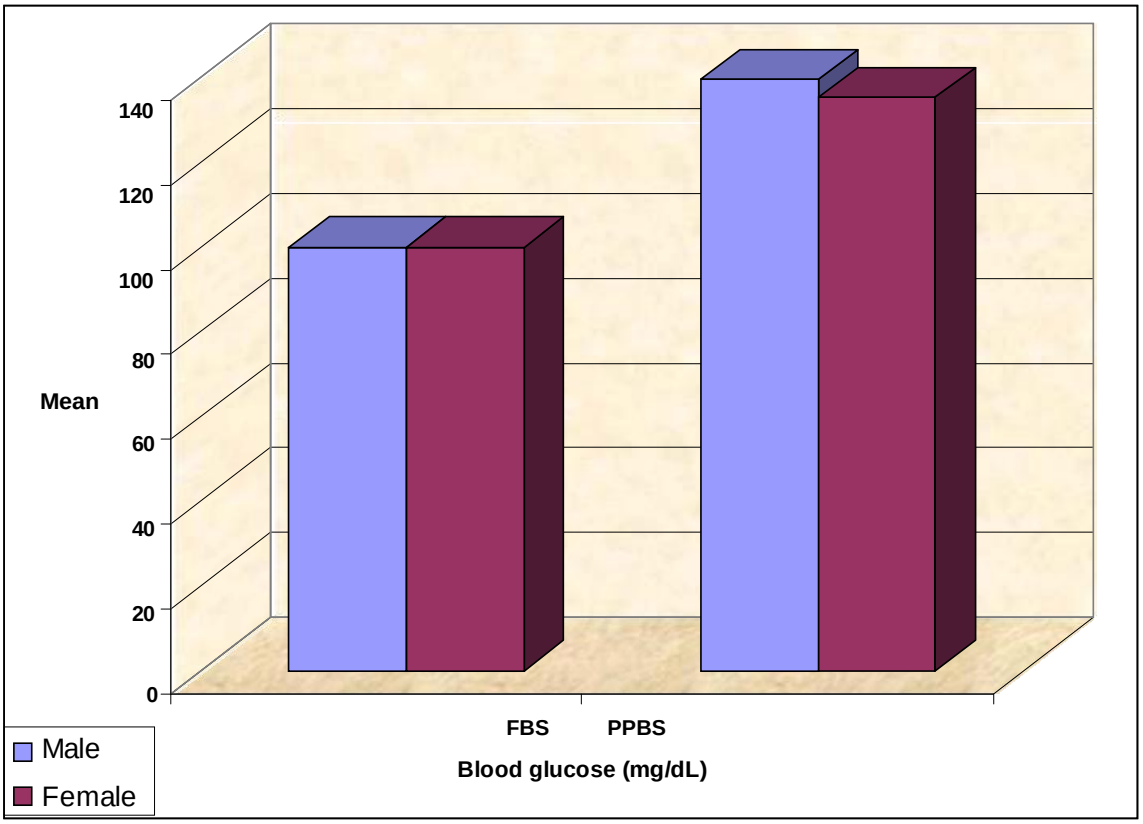
7) Blood Glucose values in the study group

Table 12: Blood glucose values in the study group

Blood Glucose (mg/dl)	Males (n=37)	Females (n=13)
FBS	100.05± 8.87	100.00±8.25
PPBS	139.54±15.81	135.23± 22.26

The mean FBS was 100.04± 8.63 mg% and mean PPBS was 138.42 ± 17.51 mg% in this study group.

Figure 11: Blood glucose values in the study group



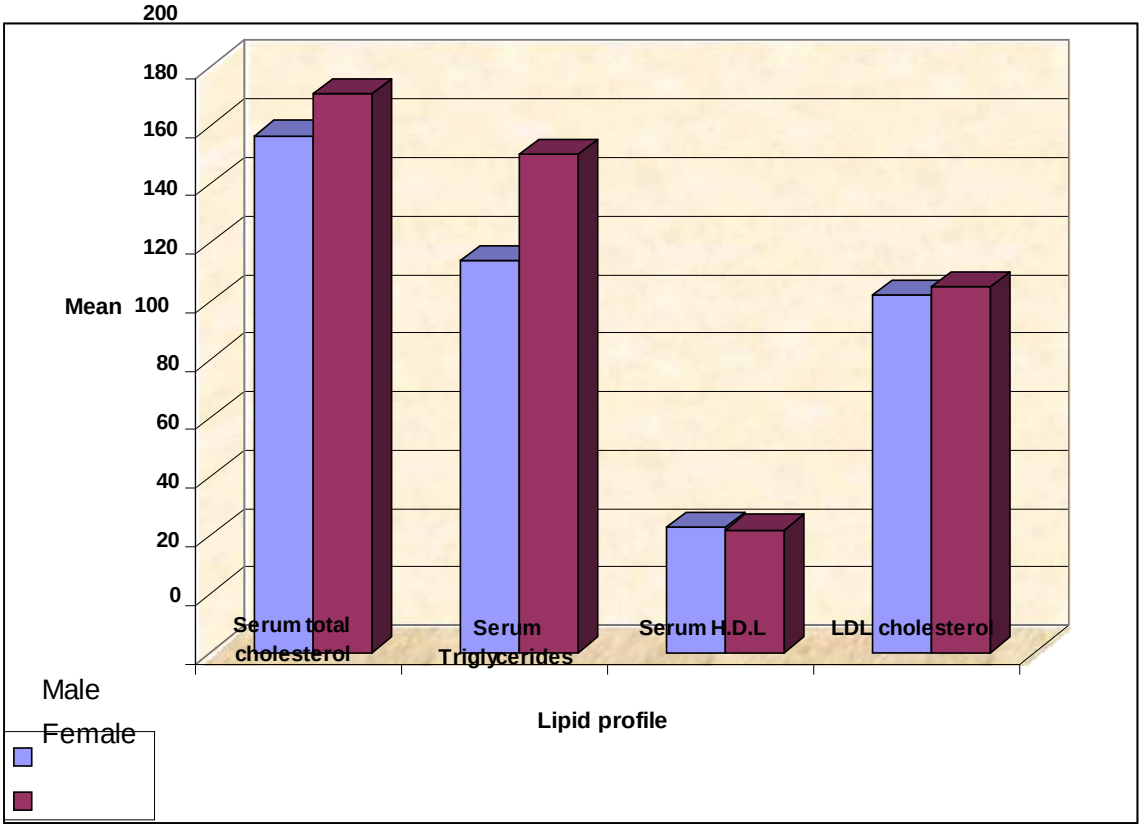
8) Lipid profile in the study subjects (in mg/dL)

Table 13: Lipid profile in the study subjects (in mg/dL)

	Males (n=37)	**Females (n=13)**
Serum total cholesterol	176.54± 22.73	190.84± 20.51
Serum Triglycerides	134± 25.37	170.00±86.71
Serum H.D.L	42.59± 2.98	41.92± 6.14
LDL cholesterol	122.00 ± 22	124.92 ± 23.47

The mean triglycerides mean total cholesterol and mean LDL – cholesterol was higher in females in this study.

Figure 12: Lipid profile in the study subjects (in mg/dL)



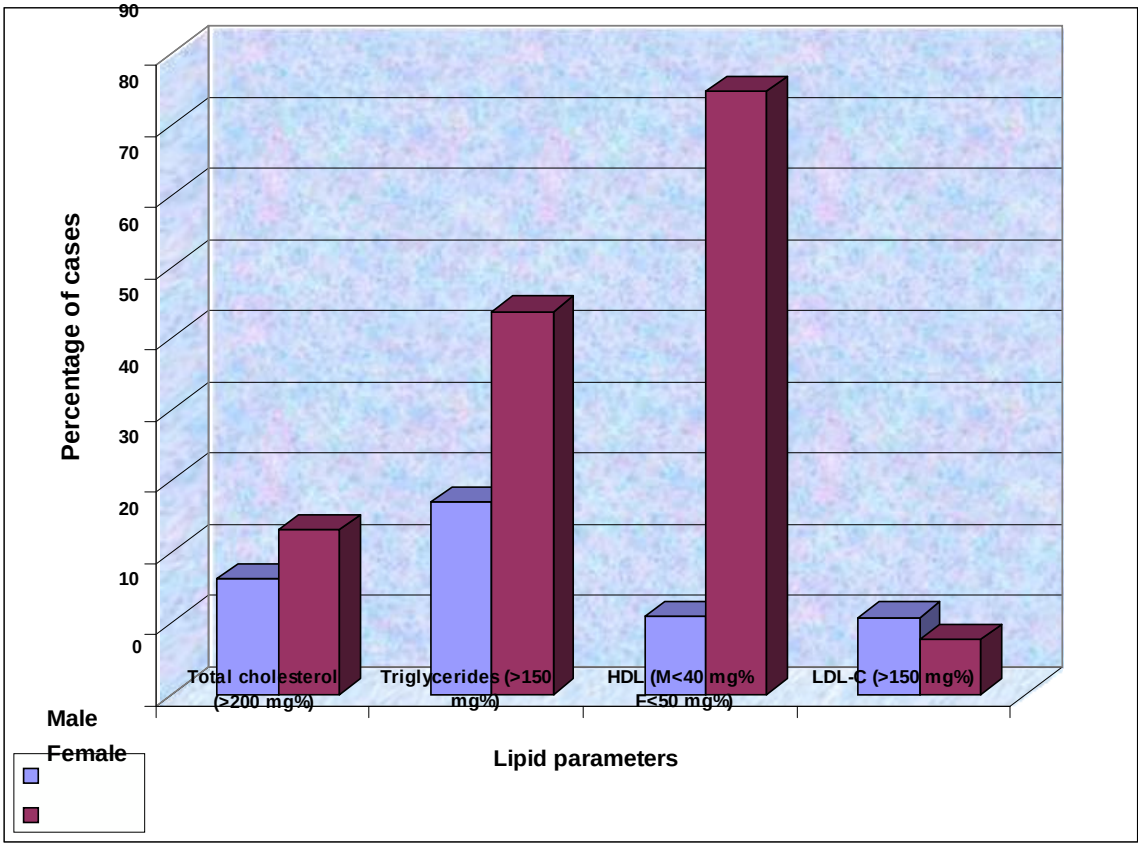
9) Abnormal lipid parameters

Table 14: Abnormal lipid parameters

Lipid parameters	Males n=37	Females n=13	Total n=50
Total cholesterol (>200 mg %)	6 (16.2%)	3 (23.1%)	9 (18%)
Triglycerides (>150 mg %)	10 (27%)	7 (53.8%)	17 (34%)
HDL (M<40 mg% F<50 mg %)	4 (10.89%)	11 (84.6%)	15 (30%)
LDL-C (>150 mg %)	4 (10.8%)	1 (7.7%)	5 (10%)

In this study the major dyslipidemia was hypertriglyceridemia (39%) and low HDL (30%) which is a typical Indian lipid profile pattern.

Figure 13: Abnormal lipid parameters



10) Microalbuminuria

Table 15: Levels of microalbuminuria (mg/day)

	Males	**Females**	**Combined**
< 30	10 (27%)	2 (15.3%)	12
30-50	16 (43.2%)	6 (46.29)	22
> 50	11(29.8%)	5 (38.5%)	16

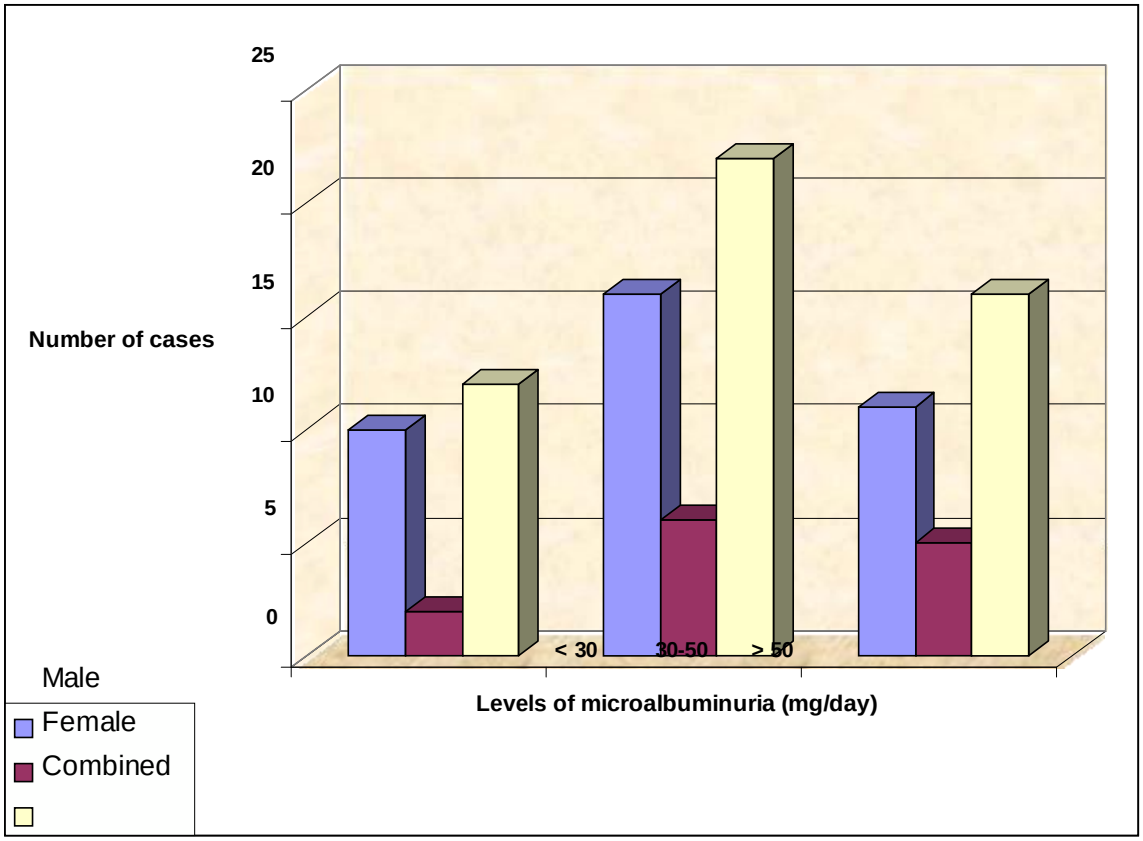
χ^2- 13.52; p<0.000

There was 27 males (73%) and 11 females (84.7%) with abnormal microalbuminuria levels in the present study.

This shows that subjects who have overt micro albuminuria had a greater chance of developing ischemic heart disease (p<0.000)

More female patients in the present study had abnormal microalbuminuria (84.7%) compared to male patients (73%).

Figure 14: Levels of microalbuminuria (mg/day)



11) Distribution of microalbuminuria in various age groups

Table 16: Distribution of microalbuminuria in various age groups

Age (years)	Albuminuria (mg/day)	
	<30	**≥ 30**
26-35	1 (25%)	3 (75%)
36-45	1(25%)	3 (75%)
46-55	3 (23%)	10 (77%)
56-65	6 (28.57%)	15 (71.43%)
66-75	1 (12.5%)	7 (87.5%)

12) Relation of Microalbuminuria with Ischemia /infarct pattern on ECG

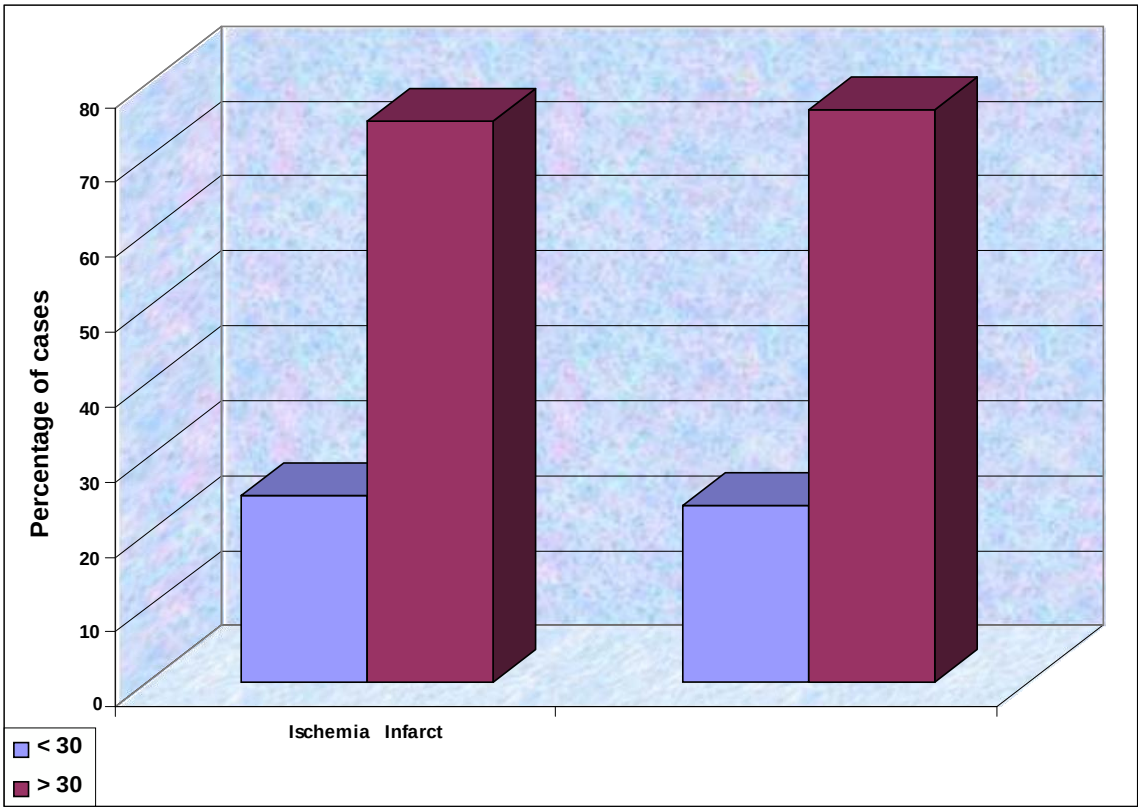
Table 17: Relation of Microalbuminuria with Ischemia /infarct pattern on ECG

	Microalbuminuria (mg/d)	
	<30	≥ **30**
Ischemia	4(25%)	12 (75%)
Infarct	8 (23.6%)	26(76.4%)

χ^2 – 13.52; p<0.000

The incidence of microalbuminuria increased with increasing age except in 56-65 age group in the present study.

Figure 15: Relation of Microalbuminuria with Ischemia /infarct pattern on ECG



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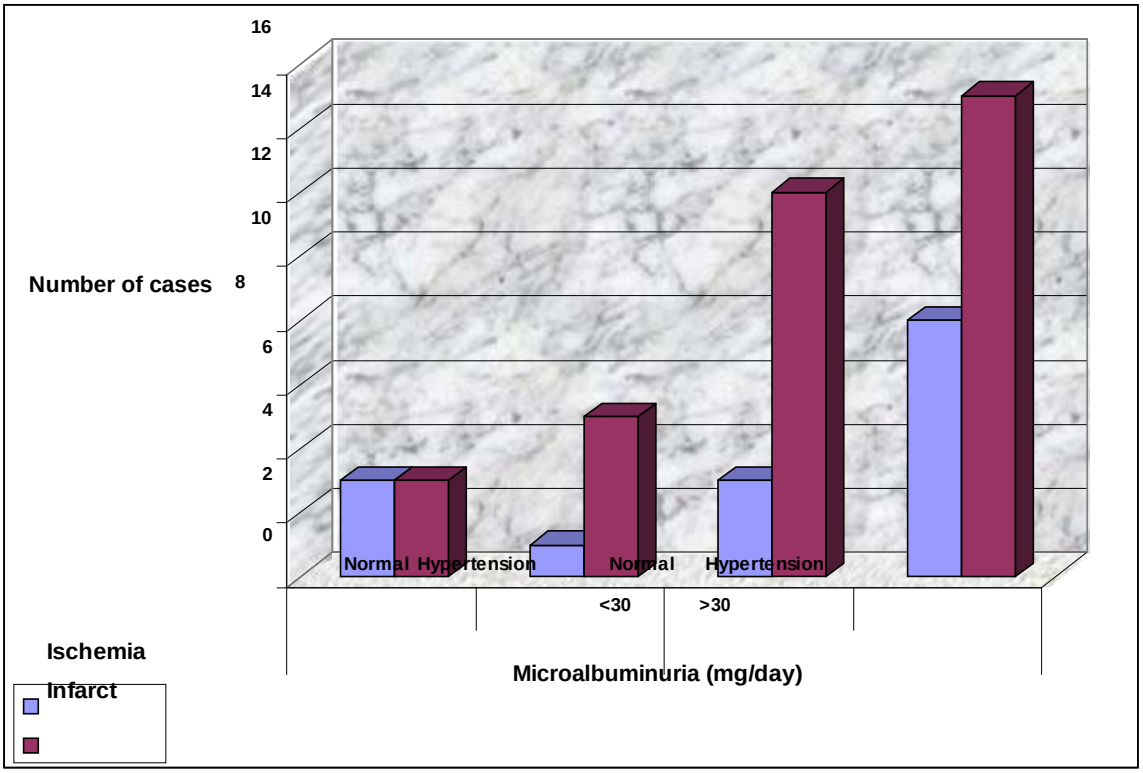
13) Relation between Microalbuminuria hypertension and ischemia/infarct pattern

Table 18: Relation between Microalbuminuria hypertension and ischemia/ infarct pattern

Microalbuminuria (mg/day)	BP	Ischemia	Infarct
<30	Normal	3	3
	Hypertension	1	5
≥ 30	Normal	3	12
	Hypertension	8	15

Out of the 29 patients with hypertension, 23 patients had microalbuminuria i.e., 79% of hypertensive patients had abnormal microalbuminuria. Fifteen out of 21 normotensive patients also had microalbuminuria (71.4%).

Figure 16: Relation between Microalbuminuria hypertension and ischemia/ infarct pattern



14) Relation between smoking, Microalbuminuria and Ischemia / Infarct

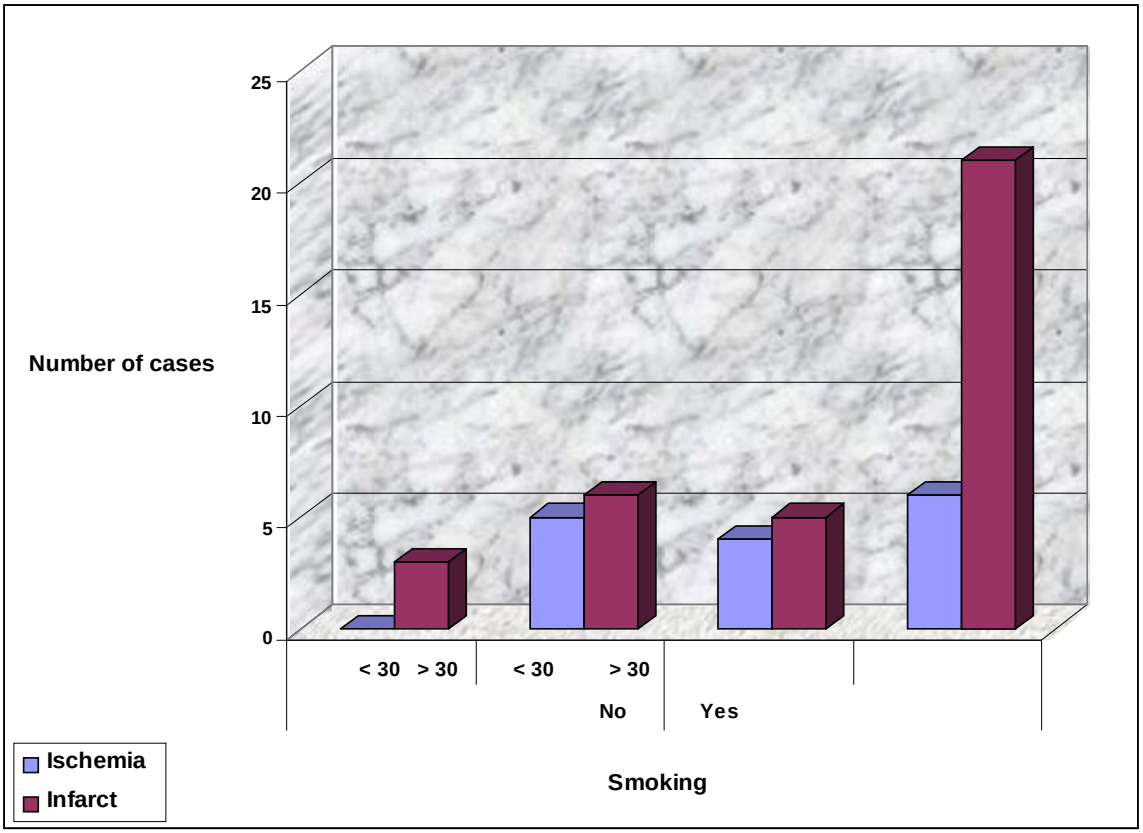
Table 19: Relation between smoking, Microalbuminuria and Ischemia / Infarct

Smoking	Microalbuminuria (mg/day)	Ischemic	Infarct	Chi-square	p-value
No	<30 ≥ 30	0 5	3 6	2.12	>0.05(NS)
Yes	< 30 ≥30	4 6	5 21	1.66	>0.05(NS)

These were 36 patients with history of smoking out of which 27 patients (75%) had microalbuminuria compared to 78% of non-smokers with microalbuminuria.

77.8% of smokers with microalbuminuria presented with myocardial infarction compared to 54.5% of non-smokers with microalbuminuria, who presented with myocardial infarction.

Figure 17: Relation between smoking, Microalbuminuria and Ischemia / Infarct



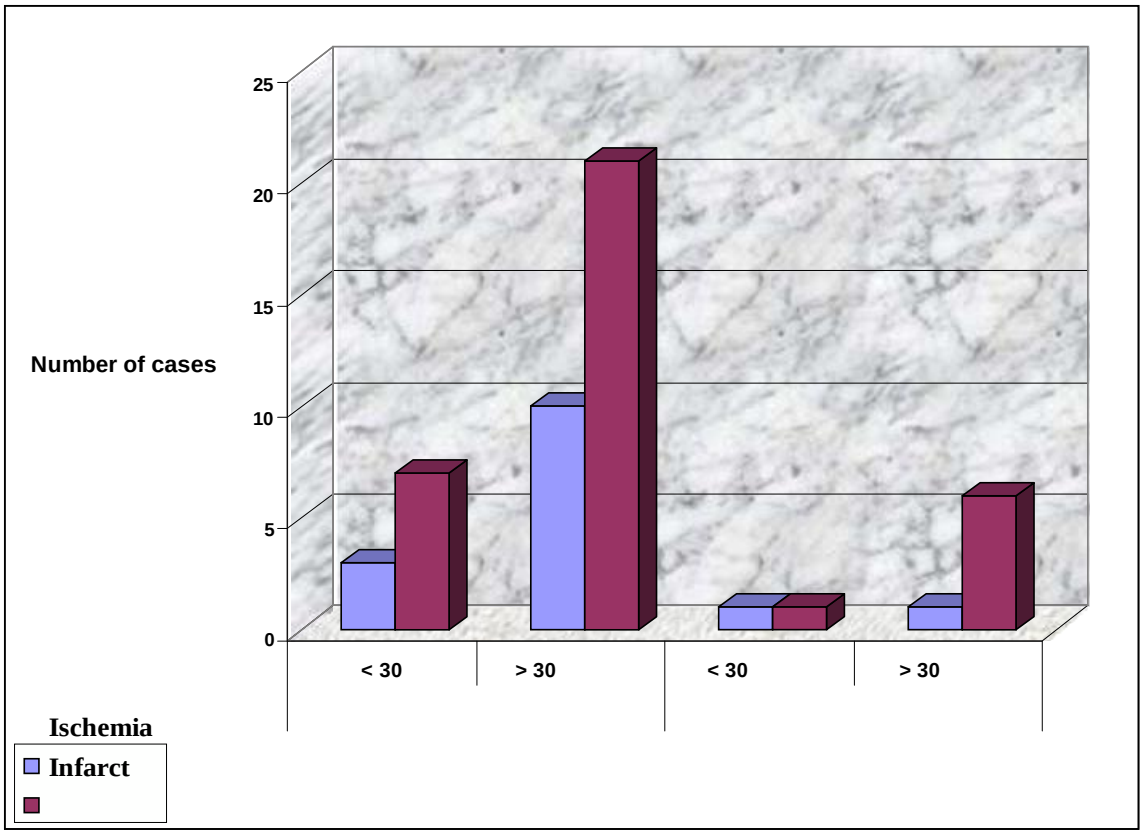
15) Relationship between total cholesterol microalbuminuria, ischemic/infarct

Table 20: Relationship between total cholesterol microalbuminuria, Ischemic/ infarct

Total cholesterol (mg/dl)	Microalbuminuria (mg/day)	Ischemia	Infarct	Chi-square	p-value
< 200	<30 ≥ 30	3 (23.1%) 10 (76.9%)	7 (25.0%) 21 (75.0%)	0.17	>0.05(NS)
≥ 200	< 30 ≥ 30	1 (50%) 1 (50%)	1 (14.3%) 6 (85.7%)	1.15	>0.05(NS)

Out of the patients with abnormal total cholesterol, 7 (i.e. 77.7%) had microalbuminuria ≥ 30 mg/day, where as out of the 41 patients with normal cholesterol 31 patients (75.6%) had microalbuminuria.

Figure 18: Relationship between total cholesterol microalbuminuria, Ischemic/ infarct

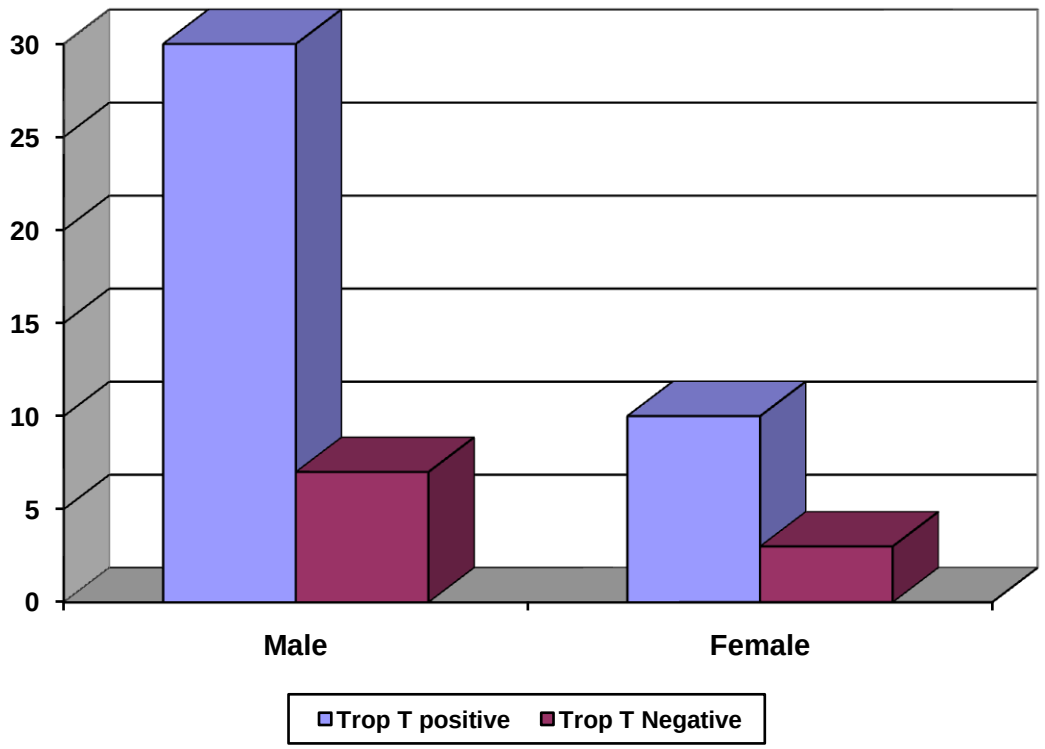


16) TROP T STATUS IN THE STUDY POPULATION

Table 21: Trop T status in the study subjects

	Males (n=40)	Females (n=10)
Trop T (+)	30	10
Trop T (-)	7	3

80% of the total patients were having Trop T positivity. 81% of males were having Trop T positivity as compared to 77% of the female with Trop T positivity

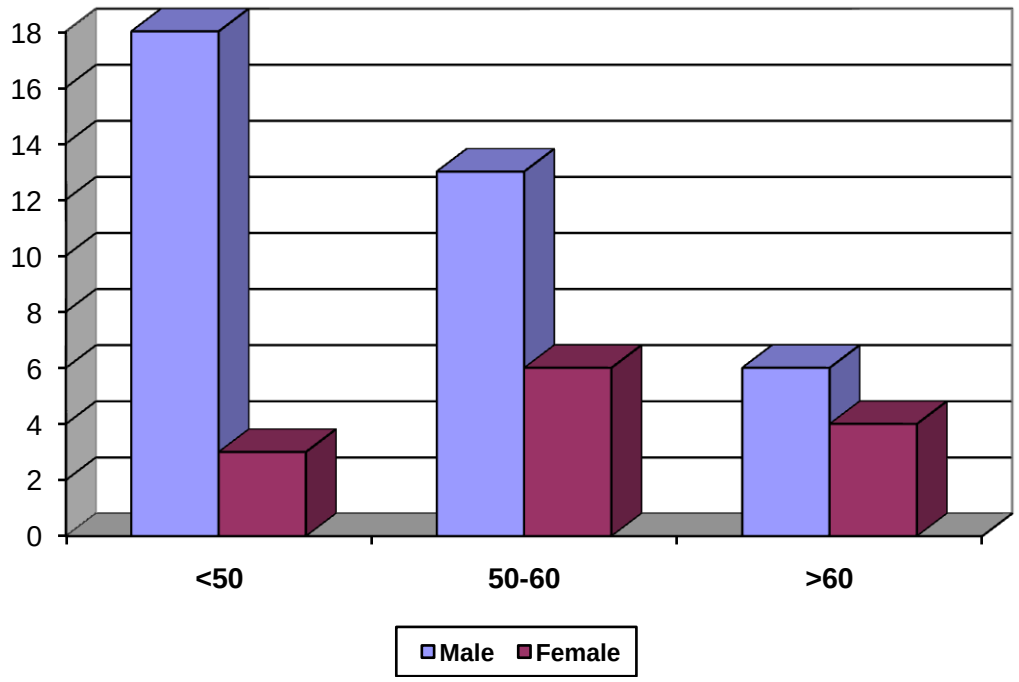


17) DISTRIBUTION OF EJECTION FRACTION AMONG STUDY POPULATION

Table 22: EJECTION FRACTION

Ejection Fraction (%)	<50	50-60	>60
Male	18	13	6
Female	3	6	4
Total	21	19	10

80% of the total patient had ejection fraction <60% of this 84% of the males had ejection fraction <60% as compared to 70% of females had ejection fraction <60%.



DISCUSSION

Ischemic Heart Disease will become a major disease burden in India by the year 2018. To target preventive strategies, risk stratification of the population should be effective. There are many reports emanating from the western literature about micro albuminuria where it is already considered in many countries as an independent risk determinant for development of ischemic heart disease[46]

Hitherto, microalbuminuria was considered as a marker of endothelial dysfunction in diabetes mellitus, but many studies have shown micro albuminuria has become an effective indicator of generalised vascular dysfunction even in non-diabetic population.[47,48]

This study was done to find out whether there is an association between IHD and MA in non-diabetic subjects.

In the present study, the diagnosis of IHD was by ECG changes. **de Bruyne MC et al**. Have shown that ECG may be used as a screening tool for mass screening of IHD in general population.[49]

This study had 74% male patients compared to 26% female patients. This is in accordance with the knowledge that males are more prone for ischemic heart disease than females.Also the **EPIC NORFLOK** study had higher male incidence which is in concordance with my study[41]

In my study the mean age of the study group was 55.68 ± 11.10 years. It was 59.92 ± 6.42 years for females. All the females were in the post-menopausal age group, which shows that sex hormones have a protective effect as far as cardiovascular risk is concerned This is in concordance with the fact that **Roeste and Banga et al** have demonstrated that urinary albumin excretion in significantly higher in non diabetic postmenopausal group when compared to pre menopausal group[50, 51]

In this study, habit of smoking was there in 72% of the study subjects indicating that smoke abuse may be an important risk factor for IHD. **Umesh N Khot et al**.had found a prevalence of 41.6% in males and 29.5% in females in their study for smoking as a risk factor[51, 59]

The BMI was > 25kg/m^2 in majority of the study group. This prevalence was much higher than that obtained by **Singh R.B. et al**.(11.0% in rural and 27.2% in urban). 58% of patients in the present study had hypertension (51.4% in males and76.9% in females). This is much higher

than the prevalence found by **Fabitz et al by STRONG HEART STUDY** (38.4% in males and 55.9% in females) but shows a similar trend[58, 59].

34% of the patients had hypertriglyceridemia and/or 30% of patients had low HDL levels, which was similar to that obtained by **Voss and Cullen et al by the PROCAM study** (39.6% of females and 34.1% of males had abnormal lipid parameters).[56, 57]

The present study showed that 76% of the patients with ischemic heart disease had microalbuminuria which shows a positive association. The **PREVEND trial** has demonstrated that that in a multivariate adjusted scenario while taking in comparison established risk determinants, the prescence of microalbuminuria was by itself having an independent association with pattern of infarct (7.2%) (OR-1.62), major type of ischemia (10.8%) (OR-1.43) and minor varieties of ischemia (15.3%) (OR-1.33).[54,55,56]

The prevalence of Micro albuminuria was estimated in 15 % of a cohort of people in the **HOPE(HEART OUTCOMES AND PREVENTION AND EVALUATION** survey which was done in the years between 1998 and 2003[52, 53, 54]

This survey revealed that 20.6% of subjects with microalbuminuria were having a higher incidence of coronary artery disease, myocardial infarction and stroke when compared with 13.8% of those who did not have

microalbuminuria.

With regard to **PREVEND trial**, 32.4% of ischemic coronary disease patients were described here, 20.8% of subjects with ischemic cardiac disease were having microalbuminuria as in comparison with 76% in this study[55,56].

This was probably because, the present study had a cohort of IHD patients in whom micro albuminuria was estimated whereas the studies mentioned above was done on the general population.

The present trial design indicate that microalbuminuria may be used as a supplementary Cardiac risk determinant even among non-diabetics and in future may supplant existing markers currently used to quantify ischemic heart disease.[57, 60].

SUMMARY

In the present study,

1. Male to female ratio was 2.85:1.
2. Subjects in the age group 56-65 years constituted 42% of the study group. 84.6% of the female patients were above 55 years of age.
3. The youngest patient in the study was 26 years old.
4. 40% of patients had a family history of Ischemic Heart Disease.
5. 80% of the patients had Trop T positivity.
6. 80% of the patients had ejection fraction <60%.
7. 72% of the patients had history of smoking. All of them were males ($p < 0.002$). 77.8% of smokers with microalbuminuria presented with myocardial infarction compared to 54.5% of non-smokers with microalbuminuria.
8. 84% of the patients had a BMI > 25 kg/m^2 (obese) and 16% were overweight (BMI 23-25 kg/m^2).
9. 79% of hypertensive patients had microalbuminuria compared to 71% of normotensive patients. 52% of patients had abnormal lipid profile hypertriglyceridemia was present in 34% and low HDL in 30% of the patients.
10. 84% of the females had microalbuminuria ≥ 30 mg/day compared to 73% of males in the present study. Microalbuminuria ≥ 30 mg/day was present in 75% patients with ischemia pattern on ECG and 76.4% of patients with infarct pattern on ECG and 76% of all cases of Ischemic Heart Disease patients ($p < 0.0001$).

CONCLUSION

Of 50 non diabetic patients with IHD were studied, 38% had microalbuminuria.

Micro albuminuria is thus positively associated with Ischemic Heart disease in non diabetic patients.

It may be regarded as an important additional risk factor for ischemic heart disease.

Hence in future aggressive screening among general population, particularly in young age group may be a worthwhile public tool for cardiac risk stratification. and targeting preventive strategies.

LIMITATIONS OF ABOVE STUDY AND SUGGESTIONS

1. 1.Only a small sample size is covered
2. ECG changes are used to screen for CAHD. Resting ECG detects only 50%of ischemia
3. It is an observational study
4. Hence further studies are needed in this regard be microalbuminuria could be cemented as a marker of ischemic heart disease

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PROFORMA

CASE NO:

A. PATIENT PARTICULARS:

Name

Age

Sex

Occupation

OP/Number IP/Number

1. Chest pain Location

Duration

Type

Radiation

Aggravating and relieving factors

Associated symptoms

2. Palpitations

Onset

Duration

Type

Aggravating or relieving factors

3. Syncope Onset

Duration

Aggravating factors

Associated symptoms (palpitations, seizures)

4. Dyspnoea Onset

Progression

Duration

Paroxysmal nocturnal dyspnea

Aggravating and relieving factors

5. Easy fatiguability

B. OTHER PRESENTING COMPLAINTS

C. PAST HISTORY

- Ischemic Heart Disease'
- Congestive cardiac failure
- Stroke
- Treatment for hypertension/bronchial asthma/Diabetes mellitus

D. FAMILY HISTORY

- Diabetes mellitus
- Ischemic Heart Disease
- Stroke
- Hypertension

E. PERSONAL HISTORY

Diet- Vegetarian /Mixed

Smoking (cigarette/beedis) - Yes/No

Alcohol - Yes/No

MENSTRUAL HISTORY:

If menopausal _____ years after menopause

F. EXAMINATION

1. Height
2. Weight
3. BMI
4. Pulse
5. Blood pressure
6. General Examination

7. Cardiovascular system

8. Other systems: a. RS
   b. GIT
   c. CNS

INVESTIGATIONS

1. Routine investigations
2. FBS, PPBS
3. Blood urea.
4. Serum creatinine
5. Fasting lipid profile
    - -TC
    - -TG
    - -HDI
    - -LDL
6. 24 hours urine micro albumin
7. 12 lead ECG
    - - Infarct pattern
    - -Major ischemia
    - - Minor ischemia
7. Treadmill testing (where indicated)
8. Cardiac enzyme estimation
9. Echocardiography-EF %

KEY TO MASTER CHART

BMI	→	Weight/height^2
DBP	→	Diastolic BP
FBS	→	Fasting Serum glucose
HDL	→	High density lipoproteins
Ht	→	Height
IHD	→	Ischemic heart disease
LDL	→	Low density lipoproteins
MA	→	Microalbuminuria
PPBS	→	Postprandial blood sugar
SBP	→	Systolic blood pressure
Sl.No	→	Serial Number
TC	→	Total Cholesterol
TG	→	Triglycerides
Wt	→	Weight.
+	→	Present
-	→	Not present

MASTER CHART

SL.NO	NAME	IP/OP NO	Age in years	Sex	Family history of IHD	smoking	HT	WT	BMI	SBP	DBP	FBS	PPBS	TC	TG	HDL	LDL	MA	INFARCT	ISCHEMIA	TROP T	Ejection Fraction (%)
1	ilangovan	1406337	34	Male	Yes	yes	168	75	26.6	130	80	96	140	186	102	40	125	78	AMI		+	55
2	chandravel	1383210	35	Male	No	yes	172	78	26.4	140	90	102	144	208	154	41	128	26	AMI		+	48
3	mohd ismail	138542	70	Male	No	yes	16	64	25	160	90	82	110	249	179	40	185	140	AMI		+	52
4	pavalingam	1378823	55	Male	Yes	yes	165	69	25.3	140	80	90	146	142	110	39	81	40	-	Yes	-	58
5	dhanakodi	1392123	61	Female	No	no	154	60	25.3	150	90	112	181	217	100	48	149	37	-	Yes	+	56
6	mariyammal	1384076	58	Female	No	no	158	64	25.6	140	90	84	115	176	141	34	113	17	IWMI		+	46
7	pankajam	1390730	75	Female	No	no	154	74	31.2	160	90	100	120	179	111	52	104	74	AMI		+	45
8	rukmani	1389049	68	Female	No	no	15	68	30.2	150	80	99	112	240	170	41	184	47	-	Yes	-	47
9	thaiyalnayagi	1388034	56	Female	Yes	no	156	58	23.8	150	80	98	120	190	441	30	130	38	-	Yes	+	53
10	vasantha	1409530	60	Female	No	no	15	60	26.7	140	80	90	114	185	192	46	100	35	-	Yes	+	51
11	subramaniam	1401342	31	Male	Yes	yes	168	74	26.2	130	80	80	110	161	119	40	97	34	AMI		+	54
12	paulraj	1416472	53	Male	Yes	yes	172	74	25	140	80	88	112	156	116	40	92	40	AMI		+	44
13	muthu	1402591	65	Male	No	yes	174	76	25.1	150	80	98	130	175	120	44	107	28	AMI		+	46
14	vadivel	1396537	48	Male	Yes	yes	166	70	25.4	130	80	100	140	202	167	49	120	71	AMI		+	53
15	anjammal	1408946	60	Female	No	no	15	68	30.2	130	90	104	150	175	146	45	102	59	AMI		-	52

16	kamaraj	145971	26	Male	No	yes	168	70	24.8	130	90	90	110	184	101	45	120	92	AMI		+	43
17	rajendran	1386485	56	Male	Yes	yes	166	72	26.1	150	90	80	110	178	187	48	92	40	-	Yes	+	41
18	Sahayaraj	1398263	50	Male	No	yes	168	75	26.6	140	80	88	108	180	110	48	124	26	AMI		+	60
19	lakshmi	1386728	54	Female	Yes	no	154	68	28.7	150	80	90	110	210	164	44	138	34	AMI		-	55
20	anbazhagan	1401284	58	Male	Yes	yes	174	80	26.4	150	90	100	138	188	114	40	138	80	IWMI		+	42
21	apaviraja	1385186	66	Male	No	yes	17	74	25.6	160	80	99	150	154	114	42	98	39	AMI		+	43
22	arokiyasami	1385648	62	Male	Yes	yes	168	72	25.5	140	80	102	140	160	120	40	120	40	-	yes	-	46
23	muthukrishnan	1388436	60	Male	No	yes	174	80	26.4	150	94	112	160	190	115	40	140	46	-	Yes	+	48
24	yasodhai	1389325	50	Female	No	no	145	60	28.5	148	100	104	140	170	100	45	120	39	IWMI	Yes	+	51
25	thambaiyan	1411487	69	Male	No	yes	166	65	23.6	150	90	114	150	180	110	44	154	70	AMI		+	54
26	dhanalakshmi	1386776	57	Female	No	no	152	66	28.6	140	100	100	134	200	168	43	140	54	-	Yes	+	56
27	asokan	1394234	40	Male	Yes	yes	168	74	26.2	130	90	104	140	200	160	44	170	38	-	Yes	+	47
28	sreenivasan	1395355	49	Male	No	yes	166	71	25.8	140	90	108	150	180	110	42	130	39	AMI		-	42
29	shanthi	121860	56	Female	No	no	15	62	27.6	160	90	110	158	176	141	35	114	28	AMI		+	43
30	thirugnanam	146330	54	Male	Yes	yes	162	69	26.3	150	80	104	142	142	110	42	90	25	-	Yes	+	45
31	sahayaraj	1398263	50	Male	No	yes	165	70	25.7	140	90	98	135	144	120	40	94	44	AMI		+	51
32	devaki	1405916	60	Female	No	no	154	62	26.1	160	100	100	148	178	154	38	120	53	AMI		+	54
33	ramaiya	1378965	62	Male	Yes	yes	166	74	26.9	170	100	108	154	204	170	44	132	48	AMI		+	60

34	ramaswamy	1382663	71	Male	No	no	164	70	26	140	100	104	160	150	134	40	110	28	AMI		+	63
35	muthaiyya	1378737	40	Male	Yes	yes	17	78	27	130	90	110	154	160	120	44	108	39	AMI		-	62
36	muthukrishnan	10448	64	Male	No	yes	164	68	25.3	140	90	100	130	184	192	44	108	40	AMI		+	63
37	uthirapathi	1389120	42	Male	No	yes	169	75	26.3	130	80	94	138	180	134	43	127	71	AMI		+	55
38	george jayapal	1389050	48	Male	No	yes	166	74	26.9	140	90	98	144	210	165	42	170	29	-	Yes	+	54
39	neelavathy	11660	60	Female	No	no	15	64	28.4	150	100	109	156	185	192	44	110	53	-	Yes	+	56
40	ambujam	1378917	40	Male	Yes	yes	17	74	25.6	140	90	110	144	175	140	38	120	27	AMI		+	53
41	kamaraj	1396537	54	Male	No	yes	162	68	25.9	160	100	101	146	180	153	40	130	45	IWMI		-	46
42	govindasamy	1409132	54	Male	Yes	yes	158	60	24	150	90	107	140	210	174	43	134	40	AMI		+	48
43	arumugam	1401310	60	Male	No	yes	164	67	24.9	140	90	103	154	178	110	50	110	24	-	Yes	+	49
44	palanimanikam	1402363	65	Male	No	yes	168	69	24.5	144	94	94	130	154	140	43	136	38	AMI		+	52
45	leninraj	1395392	70	Male	Yes	yes	158	62	24.8	150	100	99	142	160	120	42	110	54	-	Yes	+	56
46	ravindran	14033696	58	Male	Yes	yes	174	84	27.7	160	100	110	150	170	135	45	130	68	AMI		-	58
47	krishnaswami	1405453	75	Male	No	yes	163	68	25.6	164	90	104	134	175	146	40	112	70	-	Yes	+	62
48	kunjupillai	1406259	60	Male	No	yes	167	74	26.5	150	90	105	158	164	130	39	134	25	AMI		+	47
49	nagendran	1412021	60	Male	No	yes	157	68	27.6	140	90	110	170	150	124	46	108	30	AMI		-	46
50	veniktachalam	1378973	58	Male	Yes	yes	174	84	27.7	160	100	110	150	170	134	45	130	68		Yes	+	55

LIST OF ABBREVIATIONS

ACE	**Angiotensin Converting Enzyme**
ACR	**Albumin Creatinine Ratio**
ARBs	**Angiotensin Receptor Blockers**
CAD	**Coronary Artery Disease**
CRP	**C - reactive protein**
CVD	**Cardio vascular disease**
EDRF	**Endothelium-derived releasing factor**
ELISA	**Enzyme Lined Immunosorbent Assay**
HDL	**High Density Lipoprotein**
IHD	**Ischemic Heart Disease**
IL-1β	**Interleukin-1β**
LDL	**Low Density Lipoprotein**
MA	**Microalbuminuria**
NO	**Nitric Oxide**
RIA	**Radio immunoassay**
TMT	**Thread Mill Testing**
TNF	**Tumour necrosis factor**
UAE	**Urinary albumin excretion**
VCAM-1	**Vascular cell adhesion molecule**